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ANNALS OF
INTERNAL MEDICINE

VOLUME 10 JANUARY, 1937 NUMBER 7

FURTHER STUDIES ON INTOXICATION WITH VITAMIN D * †

By I. E. STECK, M.D., H. DEUTSCH, A.B., C. I. REED, Ph.D., and H. C. STRUCK, Ph.D., *Chicago, Illinois*

WITH the extensive application of massive doses of vitamin D as a therapeutic agent in various clinical conditions [1, 2, 3, 4, 5, 6, 7] numerous criticisms have arisen which may be summarized as follows:

1. Hypervitaminosis D may produce symptoms of hyperparathyroidism.
2. The therapeutic use of vitamin D is rational only in conditions of known deficiency.
3. Animals experimentally treated with vitamin D concentrates have shown extensive calcium deposits in various tissues, and other pathological changes have been found. There is, thus, danger of permanent injury to human subjects.

It is not the purpose of this paper to discuss the therapeutic value of concentrated vitamin D in any clinical condition. Only by more extensive clinical investigation can its therapeutic value be established finally.

That vitamin D in massive doses may be toxic to any individual, animal or human, has been recognized in all stages of this series of investigations which was begun early in 1929, and its administration to human subjects has been governed accordingly. It is the purpose of this paper to present evidence bearing on these questions. The first of these questions has been discussed very thoroughly by Shelling,[8] who concluded that the preponderance of evidence is against the view that the activity of vitamin D is dependent upon the functional integrity of the parathyroids and in favor of the existence of an antagonism between the two. The second criticism is purely speculative. If this idea held true very few therapeutic procedures now in use could be justified.

* Received for publication September 26, 1936.

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† This investigation at various stages has been supported in part by grants from Mead Johnson and Company; the Graduate School Research Fund, University of Illinois; the American Academy of Arts and Sciences; the Wisconsin Alumni Research Foundation; the Committee on Therapeutics of the American Medical Association; and the Phi Rho Sigma Medical Fraternity.

In considering the nature of the action of massive doses of vitamin D it is assumed that the action is very different from the physiological effects of small doses. It is so different, in fact, that the concentrated material may be considered tentatively as a different substance. At the same time there is some legitimate doubt as to the justification for this attitude.

TABLE I

Observations on Dogs Receiving Vitamin D

No.	1000 units/ K/day	Days	Kidney Mg Ca/ 100 gm. Dry Tissue	Max. Blood Ca	Microscopic		Wt. Loss Per Cent	Other Symptoms of Toxicity	
					Cell. Degen.	Ca Stain			
1	500	8	671	19.90	5	5	40	Severe	Died in coma
2	500	9	212	21.60	5	5	32	Severe	Died in coma
3	500	9	—	—	—	—	28	Severe	Died in coma
4	500	11	—	—	—	—	38	Severe	Died in coma
5	200	18	—	—	—	—	44	Severe	Died in coma
6	200	10	—	—	—	—	34	Severe	Died in coma
7	130	7	598	16.36	4	3	30	Severe	Died in coma
8	125	12	52	23.30	1	0	23	Mild	Died of distemper
9	100	30	110	16.30	0	0	7	Mild	Died of distemper
10	100	6	676	14.98	3	1	19	Severe	Died of distemper
11	100	20	—	—	—	—	23	Severe	Died in coma
12	100	13	—	—	—	—	17	Moderate	Found dead
13	60	7	340	23.36	?	0	24	Severe	Died of distemper
14	60	13	540	23.29	1	1	20	Severe	Died in coma
15	60	8	685	18.16	—	—	9	Severe	Found dead
16	60	7	800	19.56	4	2	+17	Mild	Found dead
17	60	12	865	24.50	—	—	0	Severe	Found dead
18	60	13	1221	31.06	5	5	37	Severe	Died in coma
19	60	20	—	—	—	—	42	Severe	Died in coma
20	60	10	—	—	—	—	30	Severe	Died in coma
21	50	17	3464	27.00	5+	5+	15	Severe	Died in coma
22	50	43	119	18.90	1	0	21	Moderate	Found dead
23	50	35	—	—	—	—	10	Moderate	Allowed to recover
24	50	12	—	—	—	—	28	Severe	Died in coma
25	50	24	—	—	—	—	19	Severe	Died in coma
26	48	35	47	21.50	0	0	6	Mild	Fair condition when killed
27	38	10	2200	16.02	5	5	18	Severe	Died in coma
28	37	47	115	23.16	?	0	48	Mild	Good condition when killed except emaciate
29	35	73	1148	19.30	5	5	60	Severe	Died in coma
30	35	33	693	15.60	5	5	—	Severe	Poor condition when killed
31	35	23	597	16.47	5	5	35	Severe	Poor condition when killed
32	35	8	407	22.74	1	?	17	Mild	Died of distemper
33	35	60	—	—	—	—	26	Mild	Fair condition when killed
34	35	54	—	—	—	—	40	Moderate	Found dead
35	35	30	—	—	—	—	29	Severe	Found dead
36	35	26	—	—	—	—	42	Severe	Found dead
37	25	33	1214	19.38	4	4	13	Moderate	Good condition when killed
38	25	62	131	15.80	1	1	15	Mild	Good condition when killed

TABLE I—*Continued*

No.	1000 units/ K/day	Days	Kidney Mg Ca/ 100 gm. Dry Tissue	Max. Blood Ca	Microscopic		Wt. Loss Per Cent	Other Symptoms of Toxicity	
					Cell. Degen.	Ca Stain			
39	25	70	—	—	—	—	18	?	Good condition when killed
40	25	79	—	—	—	—	8	Moderate	Found dead
41	25	50	—	—	—	—	22	Severe	Died in coma
42	25	56	—	—	—	—	5	Severe	Died in coma
43	25	16	—	—	—	—	20	Severe	Died of distemper
44	20	38	228	13.26	0	0	0	0	Good condition when killed
45	20	41	186	12.90	0	0	3	0	Good condition when killed
46	20	67	174	11.78	0	0	5	Mild	Good condition when killed
47	20	83	203	12.02	0	0	0	0	Good condition when killed
48	20	120	93	11.00	0	0	+7	0	Good condition when killed
49	20	60	—	—	—	—	0	Mild	Died of distemper
50	20	93	—	—	—	—	0	0	Good condition when killed
51	20	80	—	—	—	—	7	?	Allowed to recover
52	20	55	—	—	—	—	0	0	Good condition when killed
53	20	40	—	—	—	—	0	0	Good condition when killed
54	15	62	212	16.85	?	0	5	Slight	Died from distemper
55	15	136	147	11.83	0	0	0	Slight	Good condition when killed
56	15	70	86	12.15	0	0	0	0	Good condition when killed
57	15	153	262	10.80	0	0	+16	0	Good condition when killed
58	15	56	248	11.50	0	0	0	0	Good condition when killed
59	15	61	—	—	—	—	+12	0	Good condition when killed
60	15	61	—	—	—	—	0	0	Good condition when killed
61	15	67	—	—	—	—	0	0	Good condition when killed
62	15	90	—	—	—	—	+10	0	Good condition when killed
63	15	47	—	—	—	—	0	0	Good condition when killed
64	15	30	—	—	—	—	5	0	Good condition when killed

Early experience with impure preparations of vitamin D, particularly abroad, has led to a great deal of misunderstanding and fear of overdosage on the part of those who have had little acquaintance with the fundamental mechanisms involved. This point has been adequately discussed by Bills.[9] Suffice it to say that most of this earlier work must be disregarded when considering the effects produced by the highly purified preparations now available.

Experiments on Toxicity of Vitamin D for Dogs

The effects of massive doses of vitamin D must be judged on the basis of the dose per unit body weight and not on the absolute size of the dose. When considered in this light the order of increasing susceptibility appears to run as follows: rat, dog, human, rabbit, with little difference between the dog and human, while the rat is very much more resistant, and the rabbit much less so.

In the experiments on dogs, vitamin D was administered in the form of a solution of activated ergosterol in corn oil * (1,000,000 units per gm.) or of calciferol † dissolved in corn oil. Most of the administration was done orally. A few animals received intravenous injections in which form the material is slightly more effective. The results of experiments on 64 adult healthy dogs are shown in table 1. The daily dose ranged from 15,000 to 500,000 units per kilogram of body weight as shown in the first column. An effort was made to adjust the dose to decreasing body weight so that the ratio between the dose and the weight of metabolising tissue remained fairly constant.

The figures in the second column represent the actual number of days of administration of the vitamin D and, therefore, the number of days the animals *survived the treatment.* Usually those that did not die were killed on the day following the last dose, others within two to three days. With amounts greater than 50,000 units daily the average survival period was 12 days; with amounts between 20,000 and 50,000, 39 days; and with 20,000 units or less, 68 days.

At death, tissues were taken for chemical analysis and for microscopic examination. In an earlier report [10] on analyses of 13 different tissues in a series of dogs, it was shown that the kidney is the most vulnerable of any tissue to the calcifying action of vitamin D. In order to conserve space, only the figures for the calcium content of the kidney are included. In all other tissues the findings were very inconstant. Analyses of tissues of normal dogs have shown a calcium content in the kidneys ranging from 29 to 301 mg. per 100 gm. of dried tissue with a mean of 85 mg. The calcium content in the kidneys of 33 of the 64 dogs is shown in the third column of table 1.

With a daily dose above 50,000 units per kg. the average content of calcium in the kidney was 564 mg. per 100 gm. of dried tissue; between 20,000 and 50,000, 921 mg.; and with 20,000 units or less, 183 mg. The lower average in the first group may possibly be related to the shorter period of survival. The average in the third group is obviously lower because the dose was not great enough to cause as much deposition.

In the fourth column the figures represent the maximum concentration of

* Supplied mainly by Mead Johnson and Company, also by Abbott Laboratories, Parke Davis and Company, and Winthrop Chemical Company.

† Supplied by Mead Johnson and Company, Winthrop Chemical Company, and Glaxo Laboratories.

plasma calcium found at any time. The level was not constant in any group. Very high levels were seldom constantly maintained. In figure 1 is shown the distribution of the figures observed in dogs in relation to the daily dose of vitamin D. It is obvious that there is little correlation between the two factors. With daily doses greater than 20,000 units per kg. every animal at some time showed very high concentrations, but the level fluctuated greatly in each animal. With lower doses the figures are within the normal range for heparinized plasma.

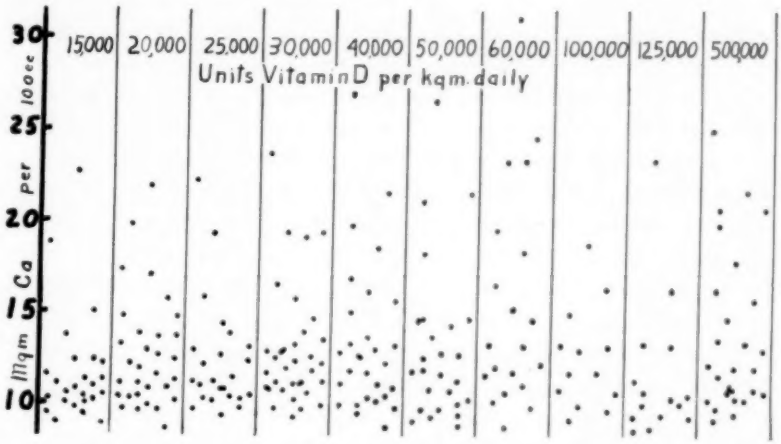

FIG. 1. The blood calcium in 43 normal dogs under treatment with vitamin D. In each column are shown the total number of determinations made on all in each dosage group. Successive determinations on the same dog appear on the same ordinate.

For purposes of simplicity of recording and comparing the microscopic findings, a scale of 1 to 5 arbitrary units was used, although this method is open to some objection. The only striking microscopic findings were degeneration of individual cells and the presence of deeply stained areas of calcium deposition. In recording the degree of cell injury, a unit of 1 indicates the presence of only occasional degenerated cells, two or three in a single field. A unit of 5 indicates a stage in which considerable masses of contiguous cells had undergone degeneration. However, this stage always occurred in conjunction with a comparable stage of calcium deposition. It will be seen that the relationship between the degrees of cell destruction, calcium deposition and calcium content of the tissue varies considerably, but that in general those tissues having the higher calcium content by analysis showed the more extensive injury. These injuries appeared first and were most numerous in the collecting tubules but later were extended quite generally throughout the organ. In only one animal were calculi found in the tubules (No. 21, table 1).

It appears that cellular injury occurs first and that calcium deposition then takes place at the sites of these injuries. In four animals (Nos. 7, 18, 27, 31) showing extensive damage to the kidney, there was no evidence of

cellular injury nor of excessive calcium deposition in any other tissue examined.

From evidence obtained on 12 other animals not included in the table, it appears that considerable loss of weight may occur before there is any evidence of injury to cells, but this was not invariably the case.

Our observations do not confirm those of Appelrot [11] to the effect that hypervitaminosis D produces medial thickening in arteries. In only four of the 64 dogs examined, i.e., numbers 18, 21, 27 and 29, was this observed. In each case there was some medial thickening in the aorta and occasionally in smaller arteries.

Loss of weight was marked in 36 out of the 43 dogs receiving more than 20,000 units per kg. per day. One retained constant weight, one gained 17 per cent. As previously suggested,[12] the early weight loss appears to be due mainly to impoverishment of fat depots. When dog No. 28 was examined at autopsy it was almost impossible to find any macroscopic fat deposits. This dog lost 48 per cent of the original weight, yet showed only mild objective symptoms of toxicity and was lively and active at the termination of the experiment. There was practically no microscopic evidence of cell injury. The plasma calcium was maintained at a higher average level over the period of the experiment than in any other animal in our experience.

On the other hand, dog No. 21 lost only 15 per cent of the initial weight, although the kidney content of calcium was higher than in any other animal. These two animals serve to show clearly that weight loss is not an inevitable accompaniment of fatal intoxication in dogs.

One of the characteristic features of fatal hypervitaminosis D is the premortal coma. This condition is usually, though not always, preceded by partial paralysis, slow, shallow respiration, fine, thready, rapid pulse, salivation, and often by psychic changes of such a nature that a previously tame, friendly dog may become unmanageable and even vicious. Very often the symptoms resemble those following an injection of oil of wormwood. This condition may persist for several days but usually appears from two to three hours before death. It is probable that all of the dogs labelled " found dead " passed through this stage during the night, but the actual train of symptoms could not be observed. None of the animals that were killed were in this stage.

The objective symptoms of toxicity were much the same as those previously described for the human,[4] such as weakness and lassitude, anorexia, polydipsia, polyuria, psychic disturbances, diarrhea. Bloody feces were passed by 11 of the 64 dogs. In addition, petechial hemorrhages were found in the mucosa of the stomach and intestines at autopsy.

With eight exceptions all of the 43 dogs receiving more than 20,000 units per kg. per day died spontaneously. Nine of these died from distemper. Of the nine, three were in such a condition that early death in coma was predictable. Of the eight exceptions, one was allowed to recover. Of

the seven that were killed, two would probably have died. The other five would probably have recovered with cessation of the treatment.

Among the 20 dogs receiving 20,000 units or less per kg. there were no evidences of cell injury, insignificant weight loss, very little evidence of toxic symptoms, and with the exception of two dogs that died from distemper and one that was allowed to recover all were in good condition when killed.

Thus, it may be concluded that vitamin D up to 20,000 units per kg. per day for periods ranging up to 153 days is not seriously injurious to normal dogs. In greater amounts there is a wide range of susceptibility entirely unpredictable from any data at present available.

That the toxic effects may be characterized as true hypervitaminosis D is proved by the fact that in four instances (numbers 7, 17, 29, 34) the vitamin preparation administered was crystalline calciferol (40,000,000 units per gm.) in solution in corn oil. This preparation contained *no* toxic by-products and yet the results were quite comparable with those from the same dose of activated ergosterol which may contain some inert material but practically no toxisterol.

In another series of experiments the dogs were brought to a stage of extreme toxicity with vitamin D and the administration was then discontinued. The state of toxicity was manifested by loss of weight, anorexia, listlessness and paralysis, and, in six animals, prostration. After varying intervals, when there was objective evidence of complete recovery, the animals were killed and subjected to the same examination as in the other series. The results are shown in table 2. In the first column are shown the periods

TABLE II

No.	Days	Recovery Days	Units/ K/Day	Kidney Ca	Max. Blood Ca	Microscopy		Wt. Loss Per Cent	
						Cell. Degen.	Ca Stain		
1	24	126	15,000	257	18.59	0	0	6	Good condition
2	15	9	20,000	48	19.89	0	0	13	Good condition
3	80	102	20,000	212	17.41	0	0	7	Good condition
4	10	48	25,000	323	22.13	0	0	30	Good condition
5	5	113	30,000	240	19.14	0	0	43	Good condition
6	5	107	35,000	242	19.43	0	0	30	Good condition
7	35	20	50,000	151	16.87	0	0	10	Good condition
8	18	115	50,000	272	14.62	0	0	29	Good condition
9	26	38	50,000	300	19.30	0	?	45	Fair condition. Still 15 per cent under weight
10	15	8	105,000	218	18.72	—	—	30	Fair condition. 10 per cent under weight

of administration of the vitamin, in the second the daily dose per kg., and in the third the recovery interval allowed. Actually in the dogs No. 4, 6, 7 and 8 complete recovery of weight was accomplished in 53, 86, 73 and 60 days respectively. Animals No. 9 and 10 were killed before weight

recovery was complete because both were definitely overweight when the experiments were begun.

Eight additional dogs were originally included in this series but all of these were in the terminal stages of toxicity described above when the treatment was discontinued, and all died within two to seven days. Six of these were already prostrate when administration was discontinued.

In all but one (dog No. 4) the kidney content of calcium was within the normal range, although all showed figures in the higher limits of the normal range except Nos. 2 and 7. The average weight loss approximated that in comparable dosage ranges in the first series.

The maximum concentrations of plasma calcium observed were all high. Microscopic examination of the tissues showed no definite evidence of calcium deposition and no cellular injury. In Nos. 2 and 5 there was some distortion of the collecting tubules in the kidney by fibrosis. No vascular lesions were found.

From these experiments it appears that dogs may recover from extreme stages of toxicity and that whatever tissue injury occurs may be reparable. In extremes the result may be fatal before repair can be effected.

In the experiments on animals reported by others, so far as the potency of the dose can be calculated, toxicity has occurred only with doses above 20,000 units per kg. per day. Since the relation of dosage to weight has not been stressed before, many other workers have failed to record data which would make it possible to calculate the dose in terms of units per kilogram.

In both of our series it is apparent that the total amount of vitamin administered is not the most important determinant of the degree of toxicity since large doses have been tolerated well over long periods while smaller doses have produced drastic effects in a few days. Nor is the magnitude of the daily dose the sole factor. In general both dogs and human subjects appeared to be less sensitive during winter months.

TABLE III

Dog No.	1	2
Units/kg./day	60,000	30,000
Initial plasma Ca	11.60	10.89
5th day	12.03	14.62
7th day	12.00	13.90
14th day	14.00	12.44
15th day	11.30	11.79
16th day	12.57	11.12
21st day	12.10	12.15
22nd day	11.34	—
23rd day	12.00	13.25
24th day	dead	—
26th day		12.24
30th day		9.70
31st day		13.00
32nd day		11.93
33rd day		dead

It has been emphasized many times that the diet is a very important factor in conditioning toxicity. All of these animals were kept on the stock kennel diet throughout and no variations were introduced at any time.

It is also apparent that the concentration of plasma calcium is not closely correlated with toxicity. Many investigators have been inclined to use the terms "hypercalcemia" and "toxicity" interchangeably. Many experiments have been done which clearly disprove a causal relation between these conditions but the two experiments reported in table 3 will serve to illustrate the point. Both of the animals showed some hypercalcemia, but it was by no means pronounced. Number 1 received twice the dose of number 2, but except for the earlier death there was no striking difference. When one contrasts these figures with the high figures for some of the animals that survived as in tables 1 and 2, it is a fair assumption that hypercalcemia per se is not the cause of toxicity.

Observations on Human Subjects

The enormous absolute doses of vitamin D that have been administered to human subjects have naturally aroused some question. If, however, one bears in mind that human and canine susceptibility seem closely approximated, and if one gives due consideration to the weight/dosage relationship, it appears that few of the human subjects have ever received amounts comparable to the highest doses tolerated by the dogs of this series.

Table IV

	Male			Female		
	Total No.	No. Toxic	Per Cent	Total No.	No. Toxic	Per Cent
Postoperative tetany	2	0	0	15	4	26.4
Hay fever and asthma	178	13	7.3	322	24	7.4
Arthritis	43	5	11.6	107	11	9.4
Miscellaneous	12	1	8.3	23	3	13
Normal subjects	63	1	1.5	8	1	12.5
	298	20	6.7	475	43	9

Total subjects	773
Number toxic	63
Per cent toxic	8

Table 4 shows the status of 773 human subjects who have received amounts of vitamin D above 100,000 units daily. The doses *routinely* given ranged upward from 200,000 units total daily dose for periods ranging from seven days to five years. With such a dose a 50 kilo subject would receive only 4,000 units per kg. per day. With 300,000 units a 60 kg. subject would receive 5,000 units per kg. per day. This table, of course, does not take into account the *varying* dosages, so that one cannot draw conclusions as to comparative susceptibility in the various groups of subjects. However, it ap-

pears, from other statistics too voluminous to include here, that the order of decreasing susceptibility among the different groups of patients is: arthritis, normal subjects, hay fever alone, hay fever with asthma, tetany.

TABLE V

Units/kg./day	No.	No. Toxic at any Stage	Per Cent Toxic
1500–3000	5	5	100
3000–5000	555	25	4.5
6000–7000	123	18	14.6
8000–15,000	70	11	15.7
15,000–25,000	16	3	18.8
25,000–35,000	4	1	25
	773	63	8+

In table 5 the incidence of toxicity at each range of dosage is shown. This analysis does not take into account the duration of administration since, as was indicated by the experiments on dogs, the total amount does not seem to be the most important factor. Nor does it take into account the effect of simultaneous administration of yeast as a protective measure which was done with many human subjects. This procedure has already been discussed rather fully.[4, 5] The first five subjects may be disregarded since they became nauseated from corn oil as readily as from viosterol, so that they do not represent true hypervitaminosis D, but rather some kind of sensitivity not related to the vitamin. It is probable that some of those subjects included in the toxic groups at higher dosage were of this type. The shortest period of administration that produced intoxication in the group on 3,000 to 5,000 units per kg. per day, was 87 days. Since the condition in this instance developed very suddenly and without any weight loss, it is possible that some unrecognized disturbance rendered the subject temporarily more susceptible. On discontinuance of administration of vitamin D prompt recovery occurred, and four days later the treatment was resumed and continued four months without further disturbance.

In the group on 6,000 to 7,000 units per kg. per day the shortest period for development of toxicity was 60 days. In this instance there was a loss of four pounds in two days. The condition was abated sufficiently to resume only after eight days without treatment. A second mild intoxication occurred three months later.

In the last two groups the high doses were not continued beyond 10 days except in one case, regardless of whether intoxication occurred. In this case one of the authors, a normal subject, took 35,000 units per kg. per day (3,000,000 units total daily) for 15 days without any evidence of disturbance of any kind.

Vrtiak and Lang[7] have recently reported 100 per cent incidence of toxicity in a series of 22 human subjects to whom massive doses of vitamin D

were administered. The discrepancy between this high incidence and the relatively low incidence in our series is difficult to explain at present.

The symptoms of hypervitaminosis D in human subjects were described fully in an earlier paper.[4] It remains now to correlate these findings with the experimental results on animals. Tentatively we suggest that the course of events is as follows: First, cellular degeneration occurs, more commonly in the kidney. Concurrently there may be loss of weight and other objective symptoms. If weight loss occurs before other symptoms it is probably due solely or mainly to increased fat catabolism. Second, deposition of calcium occurs at the sites of cell injury; apparently this does not occur except as a secondary result of such injury. Third, up to advanced stages of toxicity these processes may be reparable in dogs if the vitamin D administration is discontinued.

From the results of previously reported work [10, 12] it appears that the calcium removed from the tissues during recovery is excreted in the urine. At least, repair is not complete until the urine calcium excretion becomes normal.

The increased excretion of calcium that usually takes place [12, 13] under massive administration of vitamin D in both human subjects and dogs is not, however, due solely to removal of the microscopic deposits in the soft tissues, because the increase in the urine begins before there is any microscopic or chemical evidence of excessive deposition in soft tissues. The source of this initial increase in the urine has not yet been determined, but from Shelling's discussion it probably comes from the trabeculae of the bones. Generally the average level of blood calcium is decreased after the excretion is increased.

We have made no examination of blood pressure in dogs, but a large number of the human subjects were examined at frequent intervals over long periods. Since there have been no significant changes the data are omitted. In most instances there seems to be some tendency to a slight decrease in the general level. This, of course, does not eliminate the possibility of medial proliferation in the arterioles.

Our human subjects ranged in age from 17 to 76 years. Older subjects were generally less readily intoxicated but recovered less readily when intoxication did occur, and seemed to be somewhat more sensitive thereafter.

There are on record only two instances of death in human subjects, certainly due to hypervitaminosis D, since the more highly purified preparations became available. One of these, recently reported by Thatcher,[14] was probably a case of idiosyncrasy to vitamin D. It is difficult to determine from the report the unit dosage. However, it *is* clear that the administration was continued after intoxication was markedly developed.

We wish to stress that administration of vitamin D should be discontinued at once when the symptoms of intoxication appear. Neither animal nor human subjects in our experience have ever recovered from the toxic condition while administration continued.

The other case has not yet been reported in detail in the literature, but the reports of the coroner and the attending physician [15] reveal the following facts. A physician, aged 74, weight 290 pounds, undertook self medication with a concentrated solution of activated ergosterol. Owing to an *error* in calculation of the dosage he received 2,300,000 units daily for 18 days or approximately 18,000 units per kg. per day, a dose 10 times that intended. Since he was very obese the dose per kilogram of actively metabolizing tissue was much greater. The symptoms described were quite typical of hypervitaminosis D, with hypercalcemia, so that there is no doubt that in this case the treatment was the immediate cause of death. However, the presence of generalized arteriosclerosis suggests that this was a fundamental handicap to his recovery after discontinuing the treatment.

The administration of similar or larger amounts in our series without serious disturbance should not be interpreted to mean that such treatment can be undertaken without caution. In fact, our experience indicates clearly that administration of massive doses of vitamin D should not be undertaken for any cause except under the careful supervision of a physician who can and will carefully check the patient's condition at frequent intervals and who will see to it that the treatment is discontinued promptly on the appearance of the first signs suggestive of toxicity.

It is probable that any suggestion of kidney dysfunction should constitute an absolute contraindication. Until further information is available arteriosclerosis also should probably be considered a contraindication. Consequently, this form of treatment should be administered to older subjects only with extreme caution.

Nevertheless, if these precautions are observed, massive doses of vitamin D may be utilized therapeutically as safely as many other agents administered daily. That its misuse has resulted in death should not prejudice its controlled use under circumstances of possible value.

In view of the extensive experience in administration of vitamin D to human subjects with a relatively low incidence of toxicity, and the correlation of the results of animal experiments with the observations on human subjects, we believe that the burden of proof now rests on those who maintain the undesirability of the use of this form of therapy. Its actual practical value in particular clinical conditions will, of course, be determined only by more extensive clinical experience.

It must be admitted that the mechanism of toxicity is still unexplained. Our findings do not agree entirely with those of Ham and Lewis.[16] It is possible that the dose of approximately 600,000 per kg. per day or more, which these observers administered to rats, was a factor in producing a different type of lesion. Up to the present time conceptions of the physiology of vitamin D have perhaps been too circumscribed because of its striking effect on calcium metabolism. That the thyroid plays an important part in the action of vitamin D is indicated by the results of another investigation.[17]

Also, it appears that the pathologic effects are greatly accentuated in a hypothyroid state. This *may* be an important factor in the variability in sensitivity to intoxication.

The results obtained by Gelfan [18] on isolated frog muscle suggest that vitamin D exercises a catalytic effect in peripheral tissues. If this should be confirmed, it might serve as a forward step in explaining the injury to isolated cells in peripheral tissues. It is conceivable that the metabolism of individual cells might be accentuated to such a point as to result in the disintegration of the cells themselves. We have not been able to recognize the cellular changes preliminary to disintegration so that we can offer no explanation of the actual nature of this process.

Summary and Conclusions

1. Observations on 64 dogs and 773 human subjects receiving massive doses of vitamin D have been made and data recorded as to dose per unit of body weight, and on the nature of the process of intoxication.

2. Both human subjects and dogs generally survive the administration of 20,000 units per kilogram per day for indefinite periods without intoxication.

3. Hypervitaminosis D first produces cell injury followed by calcium deposition. This process is reversible and reparable if administration is discontinued promptly.

4. Intoxication for short periods does not result in any permanent injury that can be recognized by the methods employed in this investigation.

Addendum. After this manuscript was written there came to our attention a very comprehensive study by Cowdry and Scott [19] on normal monkeys under treatment with vitamin D in which it was suggested that pathological changes may occur in tissues without clinical symptoms. However it was also suggested that there might be a species peculiarity.

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THE DIETETIC TREATMENT OF CONSTIPATION WITH SPECIAL REFERENCE TO FOOD FIBER*

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THE non-cathartic treatment of constipation includes, among other recognized measures, treatment by diet (vegetables, cereals, fruits, fats and water), and treatment by artificial bulk producers (mineral oil, agar, bassorin, psyllium seed, cellulose and bran). In recent years the artificial products have dominated the literature and have perhaps unduly impressed the mind of the practitioner. Useful as they may be to meet temporary conditions, it is now becoming realized that these substances cannot be employed indefinitely without the possibility of some interference with nutrition (Bastedo,[2] Morgan [12]).

It therefore seems timely to refocus attention on the diet—for this after all must always remain the mainstay in treatment. Perhaps the most striking finding in examining the scientific basis for our clinical procedures in this connection is the fact that apparently no important quantitative studies on humans have made much impression on the clinical literature between the time of Rubner [14] in the eighteen-eighties to the recent publications of such physiologists as Rose,[13] Cowgill [8, 9] and their associates. Working with human subjects, as well as with experimental animals, these observers confirmed the fundamental axiom that there exists a quantitative relation between the amount of crude fiber ingested and the laxative result. Cowgill especially has clearly stated the criteria of laxation, has laid down the general procedure for the study of laxative substances on a fiber-equivalent basis, and has suggested that for normal men the physiologic fiber minimum for adequate laxation corresponds to a daily intake of 90 to 100 milligrams of fiber per kilogram of body weight. This worker confined his attention to the use of wheat bran as a laxative. In five constipated subjects two were relieved by a diet rich in fruits and vegetables, but three others required the addition of bran for comfort. It might be added that in none of the recent work is there any attempt to standardize the intake of fibrous foodstuffs in general, nor to compare the relative value of one of these articles with another.

In view of our thesis that constipation should be treated as thoroughly as possible by diet before calling upon artificial products for assistance, it would appear desirable for the physician to have a sound basis of precise information. In this regard, however, the current American books on diet are not very helpful. For even an approximate statement of the quantitative employment of diet in the treatment of constipation one must go back to von Noorden.[15] This author advocated the use of a bulky diet containing

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a daily intake of 300 to 500 gm. (10 to 17 slices) of whole wheat bread, 80 to 100 gm. of dried legumes (peas, beans, lentils) in the form of thick soup, and 10 to 15 large prunes (about 100 to 150 gm. according to our standards). This diet gave von Noorden excellent results in Germany for over 25 years. However, it is not equally practical for use in this country because of the persistent trend away from breadstuffs and legumes.

For this reason, and because of their recognized superior laxative properties, fruits were selected as the subject of our study. Prunes, apples and bananas were chosen because of their general attractiveness and availability and also for the following specific reasons: Prunes, because of their ancient repute as cathartics and the recent discovery (Emerson [10]) that they contain an active principle similar to di-hydroxy-phenyl isatin, related to the commercial " isacen "; apples, because of their wide popularity as " bowel regulators "; and bananas, because of the possibility that their smooth texture might make them particularly useful in spastic or irritated colons.

This experiment therefore was planned to determine the relative usefulness of these three fruits on a fiber-equivalent basis. The prunes, apples and bananas used in our study possessed a fiber content of 1.9 per cent, 1.4 per cent and 0.6 per cent respectively, representing a ratio of 3:2:1.*

Methods

The subjects selected for this study were nine hospital dietitians. They were in good general health and carried on their regular work throughout the course of the experiment. On the basis of their bowel function the subjects were classed as follows: Regular, three subjects (5, 7, 8); irritable, two subjects (1, 3); constipated, four subjects (2, 4, 6, 9).

All four constipated subjects showed low basal metabolic rates (exceeding minus 10), on at least one occasion. This finding, it must be confessed, surprised us and suggests an intimate relation between an individual bowel function and the thyroid secretion. It also lends emphasis to what T. R. Brown [4] has long maintained, namely, that constipation may in many instances be due to a " forme fruste " of myxedema.

The experiment was divided into eight periods of at least nine days each as follows:

Period I. Preliminary. Diet uncontrolled.

Period II. Low Fiber Basal. Fiber content 33 mg. per kg. from miscellaneous sources.

Period III. First Banana. Fiber content 33 mg. per kg. all from bananas.

Period IV. Prune. " Low Fiber Basal " plus 33 mg. fiber per kg. from prunes, making a total of 66 mg. fiber per kg.

Period V. Second Banana. " Low Fiber Basal " plus 33 mg. fiber per kg. from bananas, making a total of 66 mg. fiber per kg.

* The figures for prunes and apples were obtained from actual laboratory analysis of fruit used in the experiment. The fiber content of bananas was obtained from Circular No. 50, U. S. Dept. of Agriculture.[6]

Period VI. Apple. "Low Fiber Basal" plus 33 mg. fiber per kg. from apples, making a total of 66 mg. fiber per kg.

Period VII. Medium Fiber Basal. Fiber content 66 mg. per kg. from miscellaneous sources (see table 1).

TABLE I

Diet Used in Period VII ("Medium Fiber Basal")
Weight of subject 57.2 kg.
Total calories 2255
Fiber content 66 mg. per kg.

Distribution by Meals (Grams)	Food (Grams)	CHO	Pro	Fat	Fiber
Breakfast					
Grapefruit 125	Egg (1) 50		6.7	5.3	
Milk 200	Meat 100		20.6	11.6	
Shredded wheat 25	Milk 200	10.0	6.6	8.0	
Sugar 25	Bread 90	47.9	8.0	1.0	.45
	Shredded wheat biscuit 25	20.5	2.6	.4	.53
Dinner	Potato 200	38.2	4.0	.2	.80
Meat 100	Beets 100	9.6	1.6	.1	.90
Potato 100	Lettuce 75	2.2	.9	.2	.45
Lettuce 75	Grapefruit 125	12.6	.6	.3	.38
Mayonnaise 10	Cocoa	22.0	8.0	10.0	.27
Bread 30	(milk 100				
Butter 15	(sugar 10				
Cream 30	(cocoa 6				
Jelly 20	Custard				
Ice cream 60	(egg (½)		3.4	2.6	
	(milk 100	5.0	3.3	4.0	
Supper	(sugar 10	10.0			
Egg (1) 50	Ice cream 60	14.7	3.0	6.4	
Potato 100	Cream 60	1.8	1.3	24.0	
Beets 100	Jelly 40	30.9	.4		
Cocoa 200	Butter 40			34.0	
Bread 60	Sugar 25	25.0			
Butter 15		250.4	71.0	108.1	3.78
Jelly 20					
Cream 30					
Custard 135					

Period VIII. Third Banana. "Medium Fiber Basal" plus 33 mg. fiber per kg. from bananas, making a total of 99 mg. fiber per kg. (see table 2).

Except for Period I, which served as a control, the diets were weighed and so arranged as to fulfill the basic requirements as to caloric value, relative proportions of carbohydrate, protein and fat, and total fluid intake for the ideal weight for each subject. The fiber content was controlled throughout except in the first period, being modified from time to time according to the needs of the experiment. It also was calculated for the ideal weight for each subject. Whenever changes in fiber content were made, the caloric and basic factors were maintained by manipulating the fiber-free foods (e.g. butter, meat, milk, fruit juices) in the diet (see tables 1 and 2).

TABLE II

Diet Used in Period VIII ("Third Banana")
Weight of subject 57.2 kg.
Total calories 2284
Fiber content 99 mg. per kg.

Distribution by Meals (Grams)	Food (Grams)	CHO	Pro	Fat	Fiber
Breakfast					
Banana 115	Egg (1) 50		6.7	5.3	
Milk 200	Meat 100		20.6	11.6	
Shredded wheat 25	Milk 200	10.0	6.6	8.0	
Sugar 25	Cocoa	22.0	8.0	10.0	.27
	(milk 200				
Dinner	(sugar 10				
Meat 100	(cocoa 6				
Potato 100	Bread 90	47.9	8.0	1.0	.45
Lettuce 75	Shredded wheat 25	20.5	2.6	.4	.53
Mayonnaise 10	Potato 200	38.2	4.0	.2	.80
Bread 30	Beets 100	9.6	1.6	.1	.90
Butter 15	Lettuce 75	2.2	.9	.2	.45
Cream 30	Grapefruit 125	12.6	.6	.3	.38
Jelly 20	Cream 60	1.8	1.3	24.0	
Grapefruit 125	Jelly 40	30.9	.4		
Banana 100	Butter 40			34.0	
	Sugar 25	25.0			
Supper	Banana 315	66.4	4.1	1.9	1.89
Egg (1) 50		287.1	65.4	97.0	5.67
Potato 100					
Beets 100					
Cocoa 200					
Bread 60					
Butter 15					
Jelly 20					
Cream 30					
Banana 100					

The periods were marked off from each other by the ingestion of a capsule containing approximately 7½ grains of carmine or, if menstruation had to be considered, the same bulk of charcoal. A short basal period of three days was interpolated between successive experimental periods to allow for hangover effects. In addition the first two days of each period were disregarded for calculating laxation rates in order to discount any possible latent interval. In other words only the last seven days of each experimental period were used for the final statistics despite the fact that at least 12 days elapsed from the end of one experimental period to the end of another.

The laxation (number of stools) was recorded for each day of every period by each subject, the participants also noting the ease of bowel evacuation (subjective impression) and the character of the stools. In this paper the laxation is expressed in terms of stools per week per person.

The total colon emptying time was observed roentgenographically in five of the subjects during the first six periods of the experiment. This was accomplished by following the progress of a standard barium meal through the colon and rectum until all traces of barium were spontaneously eliminated. The opaque meal was not administered until the third or fourth day of each experimental period by which time the carmine or charcoal had been identified in the feces.

The normal total colon emptying time was determined from a review of 844 private patients previously published by one of us.[11] It was found to be 72 hours. In the preliminary (control) period only one subject showed an emptying time of 72 hours. Of the rest, three emptied in 96 hours and one in 120 hours. These figures therefore furnished the base line for the present experiment, each subject being compared throughout with her original figures.

The weight of the stools was determined in the last two periods by actual measurement immediately after passage. This served as an additional check on laxation since it was found that the increased number of stools did not always mean that a laxative effect was being produced.

Experimental Results

Period I (Preliminary). The diet was not controlled, each subject eating what she pleased but recording the following data: ideal weight (for height, age, sex); fiber intake per day; individual laxation rate.

The daily fiber intake was estimated from the individual records and was found to vary from 44 to 97 mg. per kg. The average was 68 mg., or two-thirds of Cowgill's physiologic minimum. The group laxation (seven day total for nine subjects) was 73. The laxation averaged 8.1 stools per individual per week. This period was considered typical ("normal") by all but one participant, despite the fact that the extremes of laxation varied from a maximum of 13 to a minimum of three. The total colon emptying time averaged 96 hours, with one subject taking 72 hours (ideal), one, 120 hours, and the remaining three, 96 hours for evacuation of the standard opaque meal.

There was no absolute correlation between the fiber intake, laxation, and colon emptying time. The best showing was made in the roentgen-ray group by subject 1 with a fiber average of 71 mg. per kg., laxation of 9, and colon emptying time of 72 hours. Subject 6 (not roentgen-rayed) took about the same amount of fiber, 75 mg., but had a laxation of 3. Subject 2 who felt more constipated than usual in this period had a fiber intake of 44 mg., a laxation of 10, but a colon emptying time of 120 hours. Two subjects (7 and 9) took about the same amount of fiber, 90 and 97 mg., respectively, but subject 7 had a laxation of 12 and subject 9 a laxation of 6 in this period. The four constipated individuals took 44, 55, 75, and 97 mg. of fiber respectively. The highest intake was associated with a laxation of 6.

Period II (*Low Fiber Basal*). The object of this period was to determine whether constipation could be produced at will by diminishing the fiber content of the diet to one-third the physiologic fiber minimum. Maintaining the energy and other basic requirements, the diet was prepared to supply a fiber content of 33 mg. per kg. of ideal weight—a fiber level which, according to Cowgill, should produce constipation. Such a result was indeed secured, the group laxation dropping to 58, the individual laxation to 6.4, and the colon emptying time increasing to 130 hours.

Every subject felt " constipated," the maximum individual laxation being 8, the minimum 1. The colon emptying time of subject 1 remained at 72 hours with 8 stools, but that of subject 2, also associated with a laxation of 8, was 168 hours. The colon emptying time of subject 6 (1 stool per week) was not studied because she was not in the roentgen-ray group, but was estimated as at least 240 hours.

Period III (*First Banana*). This period was introduced to determine whether bananas contained any hitherto unknown laxative quality other than their fiber (and other carbohydrate) content. In order to test this possibility, the 33 mg. of fiber (from miscellaneous sources) of the basal period were completely replaced by the same amount of banana fiber. In other words, all the fiber in this period was derived from banana exclusively. It took approximately three bananas (315 to 325 gm.) to supply this amount of fiber. The group laxation was 60, the individual 6.6, the colon emptying time 81. In short, all the findings remained the same as in the basal period except for acceleration of the colon emptying time. It should be noted in this connection that five of the nine subjects menstruated during this period. Since laxation is usually increased by this function, the acceleration of the colon emptying time should probably be considerably discounted.

In view of the above findings, it was concluded that there is no evidence that bananas possess any special cathartic value in addition to that of their fiber (and other carbohydrate) content.

The diets for the next three periods were constructed according to a uniform plan. The basal diet contained 33 mg. per kg. of fiber derived from miscellaneous sources. To this were added 33 mg. per kg. of additional fiber, derived respectively from prunes, bananas and apples, according to the fruit studied in each period. The total fiber content of the diet was 66 mg. per kg. It was decided not to exceed this level because reasonably satisfactory laxation had been produced in this group by a similar amount of fiber derived from miscellaneous sources (see Period I). Besides, it was thought that the ingestion of more than 33 mg. per kg. of fiber from a single fruit source would so overbalance the diet as to make it impractical for everyday use. Thus, for example, 66 mg. of fiber per kg. would mean 6 bananas per day, or 40 prunes, or 2½ apples.

Period IV (*Prune*). Approximately 20 small California prunes (100 gm. edible portion) a day were required to yield 33 mg. per kg. of fiber.

The group laxation was 70, the individual laxation averaged 7.7 stools per week per person, the colon emptying time averaged 91 hours. Five subjects found prunes the most laxative of the three fruits tested. Two found them second best and two rated them least effective.

Period V (*Second Banana*). The same amount of banana was used as in the first banana period, but this was in addition to the 33 mg. from miscellaneous sources of fiber. The group laxation was 62, the individual laxation averaged 6.8 stools per week per person, and the colon emptying time averaged 98 hours. One subject found bananas the most laxative fruit, three subjects gave it second place, and five subjects found it least effective.

Period VI (*Apple*). A daily average of 1¼ to 1½ cored and peeled "Delicious" apples weighing 140 gm. and served raw was required to yield 33 mg. of fiber. The group laxation was 55, individual laxation averaged 6.1 stools per week per person, and colon emptying time averaged 115 hours. Three subjects found this the most laxative period; two found it the most constipating. The remaining four found it occupying an intermediate position, more laxative than bananas, less than prunes.

The next two periods were designed to determine the effect of a diet containing the physiologic fiber minimum (99 mg.) in which one-third of the fiber was derived from fruit and two-thirds from miscellaneous sources. The first of these periods (Period VII) served as a control and contained 66 mg. of fiber from mixed sources. Banana was the source of the fruit fiber used in the last phase of the experiment (Period VIII).

Laxation was determined not only by recording the daily number of stools per subject as heretofore, but in addition by weighing the fresh stools immediately after passage. The colon emptying time was not determined roentgenologically. Each period was of nine days' duration. As heretofore the periods were marked off by carmine or charcoal and only the last seven days in each case were used in the final calculations. Five of the nine subjects who volunteered for the first six periods were used in this study.

Period VII (*Medium Fiber Basal*) (see table 1). The diet contained 66 mg. of fiber per kg. for each subject, derived from miscellaneous sources. This period served as control to the final period.

Laxation was fairly normal for the period, averaging 35 stools for the group of five, or 7 stools per person per week. The weight of the stools averaged 670.6 gm. per person per week.

Period VIII (*Third Banana*) (see table 2). The diet was the same as in Period VII, plus 33 mg. of fiber derived from an average of three bananas daily, making a total fiber content of 99 mg. per kg. for each subject. As heretofore throughout the experiment this change was effected without altering the caloric or other values of the diet.

Laxation was increased to a group level of 38 stools, an average of 7.6

stools per person per week. The weight of the stools increased to 771.2 gm. per person per week. Of five subjects tested, three showed a definite increase in laxation, and one showed practically no change. The fifth subject was apparently constipated by the banana diet. Among those whose laxation was increased was subject 6, the most constipated individual in the group. Her laxation rose from 3 in Period VII to 5 in Period VIII, and the stool weight from 385 to 740. Period VIII was rated by her equal to the apple period which had heretofore given the best laxation.

From the above experience it was concluded that the addition of approximately three bananas a day to an " average " diet (66 mg. of fiber from miscellaneous sources) is moderately laxative. The effect can be expressed as an increase in the number of stools by 0.6 per subject per week, and an increase in the weight of the stools by 100 gm. per subject per week.

Experimental Conclusions (see table 3)

According to the average laxation and colon emptying time, the laxative power of the three fruits when tested on a strictly fiber-equivalent basis (66 mg. per kg.) may be rated as follows: First, prunes with laxation of 7.7 and colon emptying time of 91 hours; second, bananas, with laxation of 6.8 and colon emptying time of 98 hours; third, apples, with laxation of 6.1 and colon emptying time of 115 hours.

Table III

Laxative Effect of Prunes, Apples, Bananas

Experimental Period	Total Stools per Week	Laxation per Person per Week	Colon Emptying Time Hours	Stool Weight Grams
I. Preliminary	73	8.1	96	—
II. First Basal	58	6.4	130	—
III. First Banana	60	6.6	81	—
IV. Prune	70	7.7	91	—
V. Second Banana	62	6.8	98	—
VI. Apple	55	6.1	115	—
VII. Second Basal	35*	7.0	—	670.6
VIII. Third Banana	38*	7.6	—	771.2

* Five subjects.

On the other hand, the number of stools was not always an accurate guide to the laxative effect because some subjects felt that as they became more constipated they required more efforts to eliminate the same or smaller bulk of stool than they would if the feces were softer. It is for this reason, for example, that subject 9 rated apples (six stools per week) above bananas (eight stools per week).

Accordingly, if subjective criteria only are considered, the fruits rank as follows: Prunes gave the best laxation in five subjects, apples in three,

bananas in one; and conversely, bananas gave the poorest laxation in five subjects, apples in two and prunes in one.

However, bananas cannot be considered constipating since in most cases they increased laxation when added to an "average" diet (total fiber 99 mg. per kg.). Similar results are reported by Bergeim [3] who found that two bananas taken before lunch and dinner and at bedtime produced daily large soft stools in three constipated subjects. In fact, owing to their smooth texture and relatively low fiber content, bananas may prove of special value in constipation associated with an irritable colon (see below).

The effect on the individuals according to their classification in terms of original bowel function may be described as follows: The two subjects with irritable colon (1 and 3) tolerated the experiment without developing diarrhea at any of the fruit periods. One of these sensitive subjects preferred the effect of bananas to that of both the other fruits tested. The three subjects classed as "regular" all preferred the effect of prunes. Of the four constipated subjects three preferred apples and one prunes. The most constipated individual (6) rated apples first, bananas second and prunes last on the basis of subjective impression.

It is probable that the simultaneous employment of several sources of fiber is superior to the use of a single variety. This is suggested by the fact that laxation was freer in the preliminary period of our experiment when the sources of fiber were freely chosen than in most of the subsequent periods when the sources were restricted.

Clinical Applications

There is no reason why the diet for constipation should not be planned with the same precision that one prescribes a diet for diabetes or for obesity. In other words the physician should be able to think in quantitative terms about fiber as he does about calories, carbohydrates, fats or proteins. Cowgill's concept of the physiologic fiber minimum should receive due recognition. The fiber content of the more important fruits and vegetables and cereals should be made more generally available to the physician.

In the accompanying tables (tables 4, 5 and 6) the fiber component is shown not only as a percentage but as it occurs in the average serving portion. By using these data the physician is now equipped to construct a diet for constipation on a quantitative basis.

According to the Cowgill standard of 100 mg. of fiber per kg. body weight, a man of 70 kg. will normally require 7 gm. of fiber daily; a woman of 55 kg. will need 5.5 gm. In order to obtain this total, selection may be made in approximately equal portions, from each of the three classes of fibrous foodstuffs—fruits, vegetables and cereals. The exact procedure may be outlined as follows, bearing in mind that only bland foods should be selected at the beginning of treatment:

1. From the list of fruits, three varieties may be chosen, preferably one

TABLE IV

Fiber Content of Cereals and Cereal Products
(Based on Edible Portion and Average Servings)

Cereals	Amount of Average Serving		Per Cent of Fiber	Grams of Fiber per Average Serving
	Measure	Weight in Grams		
Bran, prepared	½ cup	20	8.5	1.70
Bran flakes	⅓ cup	30	5.1	1.53*
Corn flakes	1 cup	25	.2	.05
Corn meal	½ cup, cooked	20 (dry)	.2	.04
Cream of wheat	½ cup, cooked	20 (dry)	.2	.04
Farina	½ cup, cooked	20 (dry)	.2	.04
Grape nuts	¼ cup	30	2.4	.72†
Hominy grits	½ cup, cooked	20 (dry)	.4	.08
Noodles	½ cup, cooked	25 (dry)	.4	.10
Oats, rolled	½ cup, cooked	20 (dry)	.9	.18
Puffed rice	1 cup	15	.1	.01
Puffed wheat	1 cup	15	1.6	.16
Rice Krispies	1 cup	30	.3	.09*
Ry-Krisp	2	15	1.3	.20
Shredded wheat biscuit	1 biscuit	30	2.6	.78
Spaghetti	½ cup, cooked	25 (dry)	.4	.10
Wheatena	½ cup, cooked	20 (dry)	.6	.12
Wheat flakes, toasted	⅔ cup	30	1.8	.54*
Wheat krumbles	½ cup	30	1.9	.57
Bread				
Crackers				
Graham	2 large	15	1.5	.23
Soda	2 large	15	.3	.05
Rye, whole	1 slice	30	1.2	.36
White	1 slice	30	.5	.15
Whole wheat	1 slice	30	1.2	.36

The above figures for cooked cereals are based on the weight of the raw material in an average serving, the average serving being a half cup.

Unless otherwise stated, the per cent of fiber was obtained from Analyses of Common Foods Bulletin No. 373, Connecticut Agricultural Experiment Station, 1934.[7]

* Fiber value obtained from Research Laboratories, Kellogg Co., Battle Creek, Mich.

† Fiber value obtained from General Foods Corporation, New York.

for each meal. Assuming that apples, prunes and bananas are taken, it will be noted that the fiber in three average portions adds up to 2.2 gm. (1.0 gm. plus 0.6 gm. plus 0.6 gm.).

2. Four vegetables should be selected including one serving of potato (0.4 gm.). If to this are added string beans (1.05 gm.), spinach (0.45 gm.) and asparagus (0.35 gm.), the total from this source becomes 2.25 gm.

3. For the cereal foodstuffs one whole grain cereal such as shredded wheat (0.78 gm.) with perhaps a slice of whole wheat bread (0.36 gm.) should be taken for breakfast. At each of the other two meals two slices of bread (0.72 gm.) may be used. This brings up the total for this group to 2.58 gm. For some of the bread other cereal products such as noodles, cake, pastry and certain puddings may be substituted.

TABLE V

Fiber Content of Vegetables
(Based on Edible Portion and Average Servings)

	Amount of Average Serving		Per Cent of Fiber	Grams of Fiber per Average Serving
	Measure	Weight in Grams		
Artichokes (French)	1 medium	30	3.2	.96
Asparagus	6 med. stalks	50	.7	.35
Beans				
Lima (fresh)	½ cup, cooked	60	1.5	.90
Snap (string)	½ cup, cooked	75	1.4	1.05
Beets (common red)	½ cup, sliced	75	.9	.68
Beet greens	½ cup, cooked	75	1.4	1.05
Broccoli	1 med. stalk	100	1.3	1.30
Brussel sprouts	⅔ cup	100	1.3	1.30
Cabbage	½ cup, raw	50	1.0	.50
Carrots	½ cup, cooked	75	1.1	.76
Cauliflower	½ cup, cooked	75	.9	.68
Celery	¼ med. stalk	40	.7	.28
Corn (sweet)	½ cup, cooked	75	.8	.60
Cucumbers	⅓ medium	30	.5	.15
Eggplant	½ cup, cooked	75	.9	.68
Kale (leaves)	½ cup, cooked	75	1.2	.90
Kohlrabi	½ cup, cooked	75	1.1	.76
Lettuce	¼ med. head	75	.6	.45
Mushrooms	½ cup, cooked	50	.9	.45
Mustard greens	½ cup, cooked	75	.8	.60
Onions	½ cup, cooked	75	.8	.60
Onions (young green)	6–8 small	50	1.8	.90
Parsnips	½ cup, cooked	75	2.2	1.65
Peas (green shelled)	½ cup, cooked	75	2.2	1.65
Potatoes	½ cup, diced	100	.4	.40
Radishes	3–4 medium	30	.7	.21
Spinach	½ cup, cooked	75	.6	.45
Squash (summer)	½ squash, 5 in. diam.	100	.5	.50
Squash (winter)	2 × 2 × 1 in.	100	1.4	1.40
Sweet potatoes	1 small	100	1.0	1.00
Tomatoes (red)	1 medium	100	.6	.60
Turnips	½ cup, cooked	50	1.1	.55

The above figures are based on the raw weight of vegetables contained in an average cooked serving, which is a scant half cup. The percentage of fiber was obtained from Proximate Composition of Fresh Vegetables, Circular No. 146, U. S. Department of Agriculture, by Chatfield and Adams, 1931.[5]

The foods used in the above example will give a daily total of 7.03 gm. of fiber. It is to be observed that in planning this type of diet slight changes may have to be made in the patient's bill of fare: (1) more attention must be paid to the choice of fruits, vegetables and cereals; (2) fruits will usually have to be substituted for the common non-fibrous desserts, such as ice cream, custard and gelatin preparations.

As regards the particular fibrous foodstuffs to be recommended, it need hardly be pointed out that clinical judgment should be the guide in practice. Common experience as well as individual idiosyncrasies should always be respected. Just because a certain fruit or vegetable possesses much fiber is

TABLE VI

Fiber Content of Fruits
(Based on Edible Portion and Average Servings)

	Amount of Average Serving		Per Cent of Fiber	Grams of Fiber per Average Serving
	Measure	Weight in Grams		
Apples (all varieties)	1 small	100	1.0	1.0
Apricots (without pits)	3 medium	100	.6	.6
Bananas	1 medium	100	.6	.6
Blackberries	1 cup	100	4.1	4.1
Blueberries	½ cup	100	1.2	1.2
Cherries	½ cup, stoned	100	.3	.3
Cranberries	½ cup, cooked	30	1.4	.42
Figs (fresh)	2–3 medium	100	1.7	1.7
Figs (dried)*	2–3 medium	75	2.4	1.8
Grapefruit	½ medium	100	.3	.3
Grapes (American type)	1 med. bunch	100	.5	.5
Huckleberries	½ cup	100	1.2	1.2
Muskmelons or cantaloupe	½ medium	100	.7	.7
Oranges	1 small	100	.6	.6
Peaches	1 medium	100	.6	.6
Pears	1 medium	100	1.4	1.4
Pineapples	½ cup, diced	75	.4	.3
Plums	4–5	100	.5	.5
Prunes (fresh)	4–5	100	.5	.5
Prunes (dried)†	3–6	30	1.8	.6
Raspberries (black)	1 cup, scant	100	3.5	3.5
Raspberries (red)	1 cup, scant	100	2.8	2.8
Rhubarb	½ cup, cooked	75	.7	.52
Strawberries	1 cup, scant	100	1.2	1.2
Tangerines	1 large	100	1.0	1.0
Watermelon	1 med. serving	150	.6	.9

Unless otherwise stated, the per cent of fiber was obtained from Proximate Composition of Fresh Fruits, Circular No. 50, U. S. Department of Agriculture, by Chatfield and McLaughlin, 1931.[6]

* Calculated from the fresh fruit.

† Fiber value obtained from California Dried Fruit Research Institute, San Francisco.

not in itself a sufficient reason for its recommendation. It is not very likely, for example, that patients able to tolerate corn, cabbage, baked beans and rough berries will consult a physician for the relief of constipation. Von Noorden was very careful to point out that only a few of the simpler fibrous foods should be used at the beginning of treatment, and that these should be continued in full doses until regular function is well established. It is only after this is accomplished that more stimulating foods may be added. Every effort should be made to avoid colic, distention and other evidences of irritation, *since the resulting spasm may serve to increase the fecal stasis.*

In any regimen for the treatment of constipation adequate water intake is essential to supply the means by which the fruit and vegetable pectins and galactans soften the feces. A daily minimum of four to six glasses (1000 to 1500 c.c.) is necessary, water taken immediately on arising being espe-

cially beneficial. An increased fat intake is also desirable but this has limitations in practice. Its chief application is in undernourished subjects where it is best taken in the form of butter, in amounts up to ¼ lb. daily. Olive oil (1 oz. two to three times a day) as such, or as " cocktail " with tomato juice or orange juice, is acceptable to some people.

A few suggestions in the practical use of fruits may be of interest. Our experience indicates that the addition of fruit in the amount of 33 mg. of fiber per kg. to an " average " diet, containing approximately 66 mg. per kg. of fiber from other sources, should relieve constipation in many, if not most, simple cases. As already explained, this amounts, for an average man, to a little over 7 gm. of fiber per day. In obstinate cases of constipation, however, the amount of fruit fiber may have to be increased considerably, additional fruit being taken between meals if necessary.

The discovery of an active principle in prunes suggests that certain fruits may possess special cathartic properties in addition to their fiber-acid-sugar content. However, our experiment fails to show outstanding superiority for prunes because only five out of our nine subjects rated them first in laxation and two reported them least effective as compared with the other two fruits studied. In any event further investigation in this direction is desirable. Prune juice is said to contain the same active principle as the whole fruit. It may therefore be more widely used as a breakfast drink either instead of or in addition to the citrous fruit juices.

Cooked apples may be substituted for the raw. Bananas may be served in any way desired, but if eaten raw they must be ripe since the unconverted starch may cause " indigestion." The criteria of ripeness are that the skin is entirely yellow and generously flecked with brown and that the pulp has softened. At this stage practically all the starch is converted into easily digested fruit sugars. Attention should be called to the fact that in the ripening process the tip of the fruit is the last portion to show traces of green color. It may therefore be used as an indicator of fitness for consumption. Obviously, it is not correct to cut off the green portion as is done in some households, and offer the rest of the unripe fruit to be eaten.

Summary and Conclusions

1. An adequate fiber intake is important in the dietetic treatment of constipation. Fiber is supplied by three classes of foodstuffs,—fruits, vegetables and cereals.

2. The relative laxative value of typical fruits was studied in human subjects on a fiber-equivalent basis. Previous work showing that the laxative effect of a diet depends largely on its fiber content was confirmed and the value of such typical fruits was demonstrated. Although prunes were found to be generally more laxative than apples or bananas, yet each of the latter proved more effective in individual cases. There is reason to believe that bananas are of special value in constipation associated with colonic instability.

3. Tables are furnished showing the fiber content of the common fruits, vegetables, and cereals, in per cent by weight and in amount per portion. With the aid of such data constipation diets may be planned on a quantitative basis.

4. In the selection of fibrous foods only bland articles should be used at the beginning of treatment because rough foodstuffs may provoke bowel irritation with resulting spasm and increase in constipation.

5. For the relief of many, if not most cases of simple constipation ordinary servings of fruit should be taken three times daily, preferably as desserts. It is suggested that the daily use of approximately 2 gm. of fruit fiber in addition to the "average" diet, containing four vegetables and some whole grain foodstuffs, suffices in such cases. This amount would be supplied for example by six prunes, one banana and one medium-sized apple. In more obstinate cases proportionately larger intake would be needed.

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THE OCCURRENCE OF CORONARY THROMBOSIS IN YOUNG INDIVIDUALS *

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CORONARY thrombosis in young adults has been generally considered of rare occurrence. There is much statistical evidence to support this opinion. Levine and Brown [1] in their classical monograph on coronary thrombosis reported 145 cases with an average age of 57.8 years. There were only three cases in this group under the age of 40, and none was younger than 35. The report of Connor and Holt [2] included 287 cases, 20 being under 40 years of age and only two under 35. Many other articles on this subject give similar statistical data as to age distribution.

Recently, however, reports have appeared in the literature indicating that coronary thrombosis is not as strictly limited to age periods beyond 40 as was previously supposed. Leary,[3] in an interesting study dealing with the pathology of coronary arteriosclerosis and its relationship to the cholesterol metabolism, includes reports on the postmortem findings in eight cases of coronary thrombosis occurring in individuals under 40 years of age, five of whom were under 35. White [4] has recently reviewed 14 cases of coronary thrombosis in individuals under the age of 40. Smith and Bartels [5] reviewed isolated case reports in the literature and were able to collect 20 proved cases in patients 40 years of age or younger, and to this group they have added two cases of their own in which the ages of the patients were 35 and 36 years respectively.

That coronary thrombosis may occur with surprising frequency in younger individuals is further emphasized by the recent high incidence of such an occurrence at the University Hospital, Ann Arbor, Michigan. Seven cases occurring in patients 35 years of age or under have been observed in this clinic during the four year period from 1931 to 1935. This group constitutes 6.1 per cent of the 114 proved cases of coronary thrombosis recorded in the files of the University Hospital.

CASE REPORTS

Case 1. L. G., a Jewish male student of 23 years, had experienced, during a period of 10 weeks prior to his admission to the University Hospital, three attacks of severe, grasping, substernal pain, radiating to the left arm, and relieved only by narcotics. Prostration, profuse perspiration and dyspnea were associated with these attacks. His past history and family history were negative. The physical examination on admission was negative. The blood pressure was systolic 122 mm. Hg and diastolic 70. The routine urine and blood examinations, including the Kahn reaction, were negative. The standard electrocardiogram taken shortly after admission is reproduced in figure 1 A. The large Q-wave with a small R-wave in Lead I,

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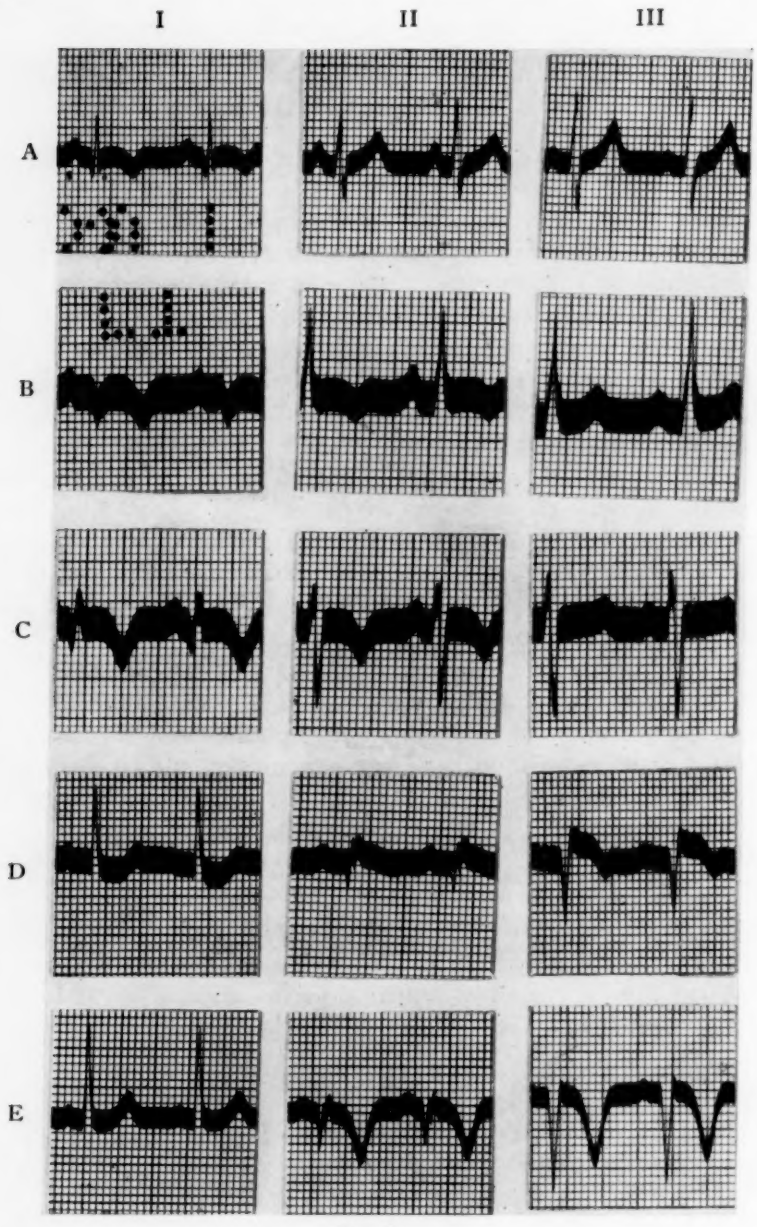

FIG. 1.

A—Case 1, standard electrocardiogram showing large Q-waves and inverted T-waves in Lead I.

B—Case 2, standard electrocardiogram showing large Q-waves in Lead I and inverted T-waves in Leads I and II.

C—Case 3, standard electrocardiogram showing large Q-waves in Lead I and inverted T-waves in Leads I and II.

D—Case 4, standard electrocardiogram, taken within a few hours of the onset of symptoms of coronary occlusion, showing large Q-waves in Leads II and III, depression of the S–T segment in Lead I and elevation of the S–T segment in Leads II and III.

E—Case 4, standard electrocardiogram, taken 22 days after acute coronary occlusion, showing large Q-waves and markedly inverted T-waves in Leads II and III.

together with the sharply inverted T_1, confirmed the clinical diagnosis of coronary occlusion, and pointed to an anterior location of the infarct. The precordial electrocardiogram (figure 2) provided evidence of an extensive anterior infarct.

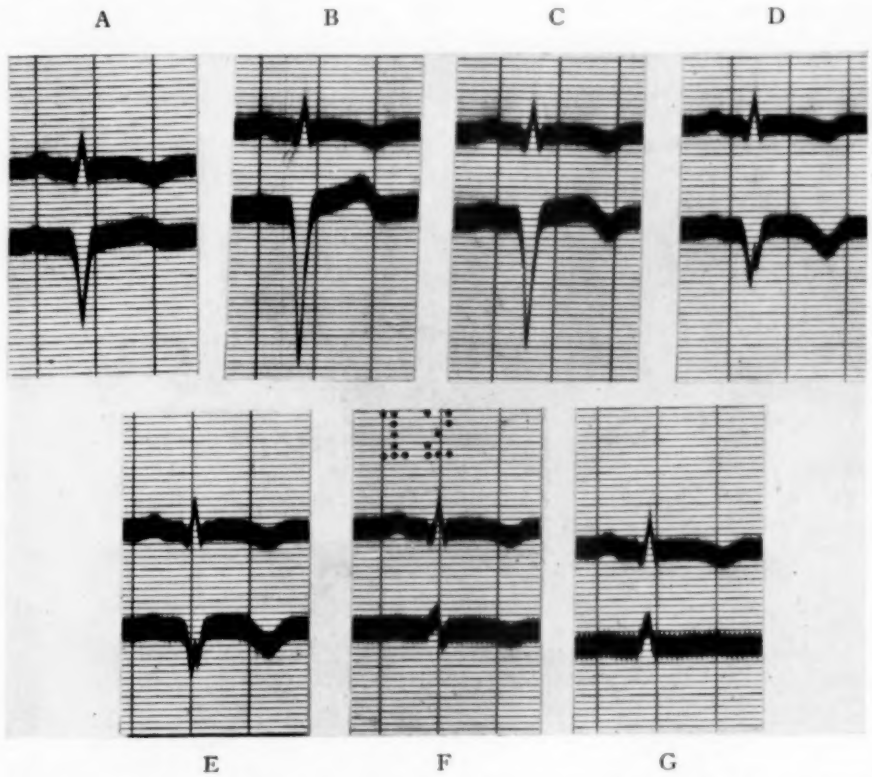

FIG. 2. *Case 1,* precordial electrocardiogram (lower curve) taken simultaneously with standard Lead I (upper curve) according to the method of Wilson, Johnston, Macleod and Barker.[8] The leads were so connected that relative negativity of the exploring electrode is represented by a downstroke.

A—5th rib at right edge of sternum.
B—5th rib at left edge of sternum.
C—5th i. c. s. mid-way between sternum and left mid-clavicular line.
D—5th i. c. s. at mid-clavicular line.
E—5th i. c. s. at left nipple line (2 cm. to left of *D*).
F—6th rib in left anterior axillary line.
G—6th i. c. s. in left mid-axillary line.

The normal initial upstroke is absent in *A, B, C, D* and *E,* a finding indicative of myocardial infarction. Note also the T-wave changes in *C, D* and *E.*

Case 2. G. K., a carpenter, aged 33, had been in good health until 10 months before admission when he had begun to notice epigastric soreness and dyspnea brought on by marked exertion and relieved by rest. Six weeks before admission, following a heavy meal, a severe attack of epigastric pain associated with vomiting, dyspnea, and palpitation had necessitated his admission to a hospital where his temperature was found to be 102.6° F. and the white blood cell count 21,600. Following this attack, anginal symptoms had been induced by less exertion than previously. The past history and family history were negative. The physical examination on

admission to the University Hospital was entirely negative. The blood pressure was systolic 115 mm. Hg and diastolic 72. The peripheral arteries were soft. The blood Kahn reaction, urine and routine blood examinations were negative. An orthodiagram showed the heart to be normal in size. There was slight widening of the base of the aorta. The standard electrocardiogram (figure 1 B) showed a large Q-wave in Lead I and sharply inverted T-waves in Leads I and II. These findings were considered diagnostic of an anterior wall infarct. The precordial electrocardiogram (figure 3) confirmed this diagnosis and demonstrated the extensive distribution of the area of infarction.

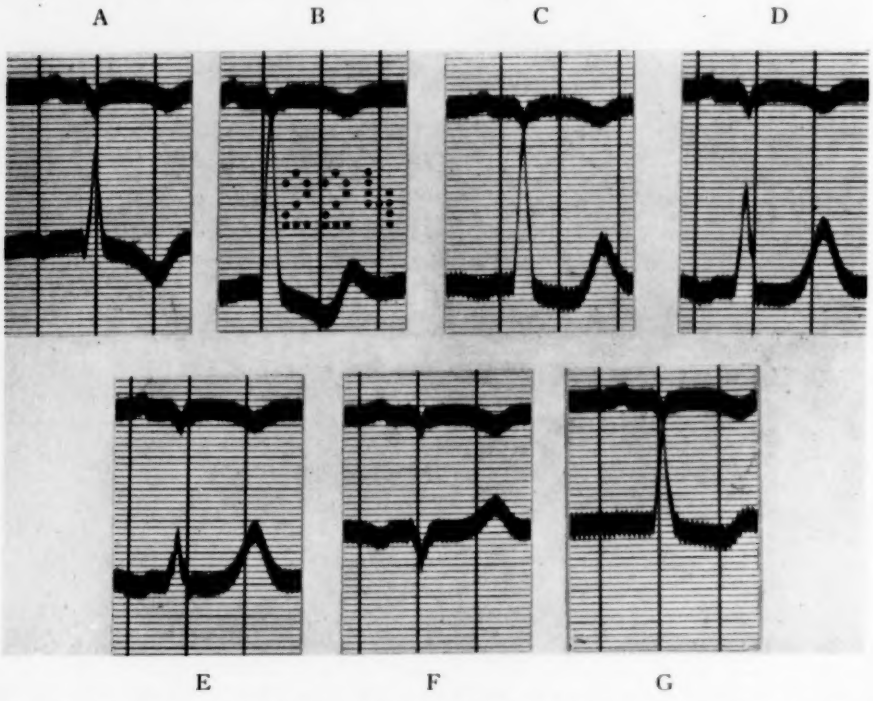

FIG. 3. *Case 2*, precordial electrocardiogram taken in the same manner as in case 1 (figure 2) except that the leads were so connected that relative negativity of the exploring electrode is represented by an upstroke.

A—5th rib at right edge of sternum.
B—5th rib at left edge of sternum.
C—5th i. c. s. mid-way from sternum to mid-clavicular line.
D—5th i. c. s. in left mid-clavicular line.
E—6th rib, left anterior axillary line.
F—7th rib, left mid-axillary line.
G—3d rib, left mid-clavicular line.

The normal initial downstroke is absent in *C*, *D*, *E* and *G*, a finding indicative of myocardial infarction. Note also the abnormal T-waves in *C*, *D*, *E* and *F*.

The patient was discharged greatly improved after a six weeks' period of bed rest. No subsequent information is available.

Case 3. J. H., a tool grinder, aged 31 years, had noted mild precordial pain on exertion or following excessive drinking over a period of two years. Two weeks before admission, he had experienced an attack of severe precordial pain radiating to the neck and down the left arm. A second attack occurred four days later and

was associated with fever, palpitation and dyspnea. The past history was negative except for three attacks of gonorrhea. He denied luetic infection. He had been married 13 years and had one child living and well. There had been no miscarriages or still-births. He had been a heavy drinker and had used tobacco to excess. The family history was negative. The physical examination was entirely negative. The blood pressure was systolic 120 mm. Hg and diastolic 70. The peripheral arteries were soft. The retinal vessels showed no abnormalities. The blood Kahn reaction, urine and routine blood examinations were negative. The standard electrocardiogram (figure 1 C), a typical curve of the Q_1T_1 type, confirmed the clinical diagnosis of coronary occlusion, as did the precordial electrocardiogram, which demonstrated a large anterior infarct.

Case 4. R. M., an auto mechanic, aged 35 years, had been in good health until one and one-half years before admission to the hospital when he had experienced severe precordial pain of six hours' duration. Except for some cardiac irregularity he had felt well following this attack until five weeks before admission. At this time another attack of severe precordial pain occurred and lasted for nine hours. Following this second attack, the patient had been unable to return to work because of dyspnea and precordial discomfort induced by exertion. The past history was negative. The family history was incomplete. Physical examination showed marked cardiac enlargement and signs of congestive failure. The blood pressure was 142 mm. Hg systolic and 100 diastolic. The blood Kahn reaction, urine and routine blood examinations were negative. A roentgenogram of the chest showed moderate cardiac enlargement and passive congestion of the lungs. The standard electrocardiogram showed a large Q-wave and a small R deflection in Lead I with a sharply inverted T_1, findings indicative of infarction of the anterior wall of the heart. Following a period of treatment, the patient was discharged and no later information is available.

Case 5. I. T., a Jewish male of 33 years, had suffered four attacks of severe, prolonged substernal pain over an eight year period prior to his admission to the hospital. Since the last attack three years previously he had complained of dyspnea on exertion and weakness. He had been a known diabetic since his first attack. The past history and family history were not recorded. Physical examination showed slight enlargement of the heart, but no other cardiac abnormality was noted. The blood pressure was 120 mm. Hg systolic and 75 diastolic. The brachial arteries were soft. The remainder of the physical examination was negative. The blood Kahn reaction and routine blood examination were negative. The urine gave a three plus reaction to Benedict's solution, but was otherwise negative. The standard electrocardiogram showed marked left axis deviation with large Q-waves in Lead I. The patient's diabetes was readily controlled on a diet yielding 90 grams of available glucose with 10 units of insulin daily. He was seen nine months later, at which time he reported marked symptomatic improvement. He had had no further chest pain.

Case 6. J. K., a 31 year old mechanic, had been well until five months before observation at which time he had begun to experience attacks of epigastric pain associated with dyspnea, nausea and vomiting. The past history was entirely negative. He had been married 11 years and had one child living and well. His wife's first pregnancy had resulted in a miscarriage. The family history was negative. The physical examination on admission revealed pupils that reacted sluggishly to light, but well in accommodation. The heart was enlarged, but was otherwise negative. The blood pressure was 110 mm. Hg systolic and 80 diastolic. The liver edge was palpable at the level of the umbilicus and was smooth and tender. The remainder of the examination was negative. The blood Kahn reaction and routine blood examinations were negative. The urine gave a three plus reaction for albumin and contained 15 white blood cells per high power field, and was otherwise negative. A

roentgenogram of the chest showed gross left cardiac enlargement and widening of the base of the aortic arch. The standard electrocardiogram showed high grade intraventricular block (QRS interval 0.13 second), large Q-waves in Lead I, inverted T-waves in Lead I, and large, broad S-waves in Leads II and III. The patient became markedly jaundiced shortly after admission to the hospital and his general condition grew progressively worse. Death occurred in two weeks. Postmortem examination revealed a localized syphilitic arteritis at the mouth of the left coronary artery with a nearly complete occlusion of the anterior descending branch. There was a myocardial infarct at the apex extending up from the apex 9 cm. on the anterior wall and 4 cm. on the posterior wall. Other findings included hemorrhagic infarction of the lungs, nutmeg liver, slight arteriosclerotic nephropathy, and acute exacerbation of chronic passive congestion of all organs. The postmortem blood Kahn reaction was positive.

Case 7. J. W., a 33 year old metal polisher, was admitted to the University Hospital with anasarca of one month's duration. Four abscessed teeth had been removed one month before the onset of the generalized edematous condition. The patient had had whooping cough, diphtheria, tonsillitis, and possibly scarlet fever in childhood. The family history was negative. Physical examination showed considerable pallor. The tonsils were medium sized and did not appear infected. The eye-grounds appeared normal. The cardiac examination was negative. The blood pressure was systolic 190 and diastolic 110. There were signs of fluid at both lung bases and in the abdomen. The legs were edematous. The blood Kahn reaction and routine blood examinations were negative. The urine showed four plus albumin, and several red and white blood cells per high power field, and 10–30 casts per low power field. The blood non-protein-nitrogen was 37.5 mg. per cent. Five days following admission, while having his back rubbed, the patient developed severe substernal pain. This pain lasted five days and was relieved only by morphine. There was considerable dyspnea with the attack. The temperature and white blood cell count were elevated. A series of electrocardiograms showed changes characteristic of infarction of the posterior wall of the heart. Two of the electrocardiograms have been selected and are reproduced in figure 1 D and E. Several months after the attack of coronary occlusion, and while still in the hospital, the patient developed severe pleuritic pain associated with fever. Death occurred one week later. Postmortem examination showed an occlusion of the right coronary artery 3 cm. from its origin. There was extensive infarction of the posterior wall of both ventricles extending into the septum. The lungs showed hemorrhagic purulent pneumonia. There was an early subacute glomerulo-tubular nephritis with lipoidosis of the tubular epithelium.

Comment

Coronary occlusion in older individuals is ordinarily the result of degenerative changes associated with advancing age. What factors were responsible for the premature coronary changes in the patients above described is an interesting and important question. Factors of recognized importance are syphilitic infection, hypertension and diabetes. In four of these patients the explanation may be wholly or partly on the basis of one or the other of these factors. In two of them, cases 4 and 7, hypertension undoubtedly played a part in the development of the coronary condition. Diabetes may be held partly responsible for the premature occurrence of severe coronary disease in case 5. In one patient, case 6, syphilitic infection involving the mouth of the left coronary artery was responsible for the oc-

clusion and resultant infarction of the myocardium. The finding of infarction of the myocardium in this patient is emphasized inasmuch as it is a rare complication following the occlusion of an orifice of a coronary artery or stenosis of one or both orifices by the syphilitic process (Von Glahn [6]).

There remain three patients (cases 1, 2 and 3) in which the etiological factors above mentioned were entirely lacking. The basis for the premature coronary disease in them remains obscure. An attempt has previously been made to explain cases of this type on the basis of an inherited susceptibility to arterial degeneration. Musser and Barton [7] have advanced the hypothesis that there are two distinct expressions of coronary disease. One is observed in elderly individuals, representing largely the effect of senescence. The other is said to be observed in younger men with a familial tendency to coronary disease. A review of the family histories in the three cases under consideration reveals no familial tendency.

It is of interest in reviewing the entire group of seven cases to note that all the patients were males, none was overweight, none was engaged in a professional occupation and in none, except the patients with nephritis and syphilis, did infection appear to play a part. Five of the seven patients were engaged in occupations requiring hard labor. Only one patient (case 3) reported having used tobacco to excess.

The mortality of the acute attack of coronary thrombosis in these cases was unusually low. Five of the seven cases survived their attacks by at least six weeks. Subsequent information is not available except in case 5, in which case the first attack had been survived eight years.

Summary

Coronary thrombosis in young adults, although generally considered to be a rare condition, may occur with surprising frequency. Seven cases in patients ranging in age from 22 to 35 are reported.

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THE ESTIMATION OF CARDIAC FUNCTION BY SIMPLE CLINICAL METHODS *

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THE problem of determining the functional impairment, or conversely the cardiac reserve of ambulatory cardiac patients has always been a baffling one. Even with the use of all our modern laboratory adjuncts—the fluoroscope, roentgen-ray measurements of the heart, and lastly the electrocardiogram, in addition to all available clinical methods, one is often at a loss to decide just where in the scale of impairment of cardiovascular function a particular patient belongs. This difficulty of course arises chiefly in the case of the strictly ambulatory cardiac patient, since those patients who show evidences of *decompensation* either at rest or after moderate activity all plainly belong to Class III of the American Heart Association's functional classification.

It is in attempting to differentiate between Class I patients, "those with organic heart disease manifesting no significant disability for the ordinary activities," and Class II A patients, "those manifesting ability to perform with slight impairment," and between the latter Class and Class II B patients, "those with considerable impairment of ordinary activity," that one is confronted with many pitfalls. For the criteria on which we are prone to base our differentiation are in the main purely subjective symptoms, and as Libman has so ably pointed out, the sensitivity (and consequently reactivity) of different individuals to noxious and painful stimuli is extremely variable. The use of our recently acquired laboratory adjuncts to cardiac diagnosis often (though certainly not always) helps us to determine objectively to some degree how much actual disease is masked or magnified under a cloud of subjective complaints.

But these measures are usually not available to the average medical examiner, and he must form his judgment as to the cardiac efficiency of his patient solely on the information obtained by his eyes, hands, ears and a critical mind. Yet upon this judgment must be based prognostic determinations as to the insurability of the patient, disability estimates for compensation purposes, and last but not least therapeutic decisions. Shall he tell the stolid unsuspecting laborer before him, in whom he has found a well-defined organic murmur, that he is a "cardiac" and must change his occupation and otherwise lead a restricted and closely regulated life; or shall he casually inform him that the examination has revealed a "slight leak" which is of little importance, and requires him to make little or no change in his mode of living, beyond observing the ordinary precaution of having a

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periodic medical examination? The fallibility of basing such decisions merely on the character of the murmur is too evident to require elaboration here. It is the purpose of this paper to show whether, and if so, to how great a degree, the facts elicited on an ordinary clinical physical examination can be relied upon in estimating the degree of cardiac disability in these types of cases. This will be done by showing the amount of correlation existing between certain readily observable clinical data and the evidences of myocardial damage furnished by the laboratory.

The writer is well aware that various and numerous so-called " effort " and " cardiac function " tests have been put forward in the past. Many of these are not suitable in that they do not represent the ordinary activities of the individual's everyday life (such are spirometer, flarimeter, etc.). All of them are deficient in that no two individuals can be expected to exert the same degree of effort in performing the same tasks. One will walk up and down the prescribed number of steps with vigor, another in an ordinary manner, and a third gingerly or lackadaisically. Similarly in hopping tests, in spite of explicit directions, one will barely more than timidly raise his heels off the floor the required number of times, another will more or less closely approximate the " 50 hops—3 inches off the floor—at one second intervals," while a third will leap with great abandon as high as he can off the floor until he is abruptly restrained. The writer proposes no new variation of the exercise tests, as he believes the above sources of inaccuracies are in the main unavoidable. However, since a quantitative equality of the amount of exertion in various individuals cannot be attained, we have tried to avoid as much as possible a quantitative comparison of the results. Instead we have stressed the qualitative relations of the cardiorespiratory adjustment to exercise,— that is, not " exactly how much " the pulse and respiration have increased after exercise, but rather " in what manner " the proportion between pulse and respiration has varied after exercise as compared with the proportion before exercise.

Methods: In these studies the following technic was closely followed. The patient's pulse and respiration were taken while he was standing at rest. After the patient had been still long enough for stable rates to be established (generally after a wait of 15 to 30 seconds), the cardiac apex rate was counted (with the stethoscope) for 10 seconds, and immediately thereafter (with the stethoscope still on the chest) the respirations were counted for 15 seconds. These short periods of counting were used because experience showed that the maximal rate changes generally occur very rapidly and subside very rapidly. The patient was then asked to hop 50 times (25 times on each foot), and immediately thereafter the pulse and respiratory rates were taken in exactly the same manner. The auscultatory method of counting both the rates was used exclusively as it was found to be more accurate than the palpatory method, and because it did not interfere with the simultaneous observation (on the " second " dial of a watch) of the elapsed time

intervals, as a visual method would have done. Since all the observations were made by the same examiner, individual differences in the technic were reduced to a minimum. At this point it may be stated that " sitting resting rates " and " rates three minutes after," and in some cases " rates two minutes after " the completion of the exercise were also taken routinely on all cases. These data, however, will not be considered in this study as it was soon found that there were no significant differences in these factors in many cases of even obviously greatly differing functional cardiac capacities. (For example, a case of marked valvular disease with evident functional impairment was quite as apt to show no elevation of the pulse and respiration three minutes after exercise, as was a case with no cardiac lesion.) Although, as hinted above, 50 hops were routinely asked for, in certain cases more or less were required as it was felt that only exercise sufficient to cause manifestly increased respiratory effort would serve to bring out the qualitative differences mentioned in the previous paragraph.

Why were the criteria just indicated, namely, tachypnea and the pulse-respiratory ratio after exercise, chosen to the exclusion of others? Simply because other criteria are not readily measurable from a practical standpoint. This criticism applies to the usually stressed " dyspnea " or " shortness of breath " and equally to " cyanosis " which necessarily must be subjectively estimated by the examiner. The other definite clinical criteria of impaired cardiac function, namely edema, hepatic and pulmonary congestion, marked cardiac irregularities such as fibrillation, and of course extreme dyspnea and cyanosis, as well as characteristic angina, all are found only in cases that offer no problem for functional classification—they all belong definitely in Class II B. Such cases not only do not usually require a cardiac function test for the demonstration of their disability, but actually may be hazardous subjects to put through such an ordeal.

Clinical Material: The material on which these studies were made comprised ambulatory out-patients examined by the writer, consecutively, over an 18 months' period (from September 1931 to May 1933), at the Veterans' Facility at Lyons, New Jersey. They were all veterans, being examined in regard to claims for disability compensation, disability allowance, or insurance purposes. The great majority were veterans of the World War, —the remainder veterans of the Spanish American War and allied expeditions. Data for this study were collected on 209 cardiac cases, and on 101 non-cardiac controls. A substantial majority of the patients had been previously examined by other Veterans' Bureau examiners, and in the occasional instance where there existed a significant discrepancy between the findings in the earlier and in the later examinations, no change was made in the diagnosis unless the later findings were confirmed by a consultant examiner (Dr. J. E. Maloney). Occasional patients returned for re-examination during the 18 months' period of the study thus permitting a personal checking of the earlier findings. The ages of the patients under

consideration ranged from a minimum of 29 years for the World War veterans to a maximum of 64 years for the Spanish War veterans. Although the clinical impressions which are the result of this study were derived as a result of the observation of all the 209 cardiac cases and the 101 non-cardiac controls, the statistical corroboration of these impressions will be based only on those 65 cases that were worked up completely from a laboratory as well as clinical angle, viz., those cases in which complete electrocardiographic and roentgenological studies were made in addition to the usual routine clinical physical examination and urinalysis. The following table will indicate the pathologic-anatomical division of the material. It will be noted that the completely worked up cases are listed under the heading, " Complete Data Cases."

TABLE I

Key Letters	Pathologico-Anatomical Type	Total Number of Cases	Number of "Complete Data Cases"	Average Age
Rm	Rheumatic heart disease, typical mitral stenosis and regurgitation	52	18	38.5
Ra	Rheumatic heart disease, aortic valvulitis (stenosis or regurgitation or both)	15	4	42.3
Ra and m	Rheumatic heart disease, combined aortic and mitral valvulitis	38	10	35.3
M	Pure mitral regurgitation	26	8	39.9
H	Hypertensive heart disease	41	6	41.
A	Arteriosclerotic heart disease	14	6	44.2
L	Luetic heart disease	7	3	36.3
E	Emphysematous heart disease	2	2	53.5
F	"Functional" heart cases	14	5	42.2
	Totals	209	62	
X	Non-cardiac controls	101	3	

It should be explained that Class " M "—" Pure Mitral Regurgitation " —is not to be considered a specific pathological-anatomical group. Undoubtedly a large proportion of these cases correctly belongs under the " Rheumatic " heading. However, since it is impossible to obtain an accurate history with this type of patient, the writer prefers to list only those cases with typical auscultatory and palpatory findings under the rheumatic classification. The " functional " group is also a rather miscellaneous one, and includes such diagnosis as " essential tachycardia "; " neurocirculatory asthenia "; " tachycardia with severe diabetes "; " myxedema heart "; " alcoholic tachycardia "; " pseudo-angina pectoris," etc.

The average age of 90 non-cardiac controls was 38.4 years, and of 54 " Complete Data " cardiac cases—39.5 years.

Results: As these studies progressed, the writer began to feel that a triad of clinical signs often appearing after ordinary exercise, could be taken as fairly reliable indices of cardio-respiratory embarrassment, and inferentially,

in those cases in which no respiratory disease or other obvious cause of increased pulse or respiratory rate was detectable, the occurrence of these signs pointed toward the existence of organic heart disease with definitely impaired function. These signs were: (1) Tachypnea, an increase of the respiratory rate immediately after exercise to 24 or more per minute; (2) a " paradoxical pulse-respiratory ratio," i.e., a ratio of pulse rate to respiratory rate which is not greater after exercise than before; (3) a diminished pulse lability as indicated by the presence of a pulse/respiratory ratio after exercise which is less than a certain critical minimum norm determined for this age group to be 4.5. The first of these signs was found to be the one most frequently observed, but the third sign is probably that of greatest significance.

In order to show how the " critical " norm for the pulse/respiratory ratio was determined it will be necessary to consider first the results obtained in the study of the 101 control cases. These comprised 101 veterans belonging to an essentially similar age group as our cardiac cases, but suffering from no detectable cardiac or respiratory disease. These cases were all put through the same exercise routine described above and the same pulse and respiratory readings were taken. Of these 101 cases, 74 showed no tachypnea after the prescribed exercise. On the other hand 27 control cases did show tachypnea (a post-exercise respiratory rate of 24 or more). Since cardiac and respiratory disease were presumably ruled out in these cases, it is necessary to explain this tachypnea on the bases of so-called " nervous " or " emotional " factors. Apparently by far the commonest evident etiological factor was the presence of physical disabilities that were obviously inducive of pain when the prescribed exercise was performed. Such disabilities varied from common conditions such as painful flat or weak feet, herniae, sacro-iliac disease, various grades of arthritis particularly of the lower extremities, to comparatively rare disabilities such as thromboangiitis obliterans. All but some five of these control cases showing tachypnea presented lesions that would be patently pain provoking under the prescribed exercise. Only these few then need be explained on " nervous factors." The writer is so impressed by the frequency of tachypnea in painful conditions, that he believes the presence or absence of an increased respiratory rate may be taken as a fairly reliable objective index of the presence of pain in cases where malingering may be suspected.

To return to our main thesis, however, we found that the average post-exercise pulse-respiratory ratio after exercise for the 74 control cases that did not exhibit tachypnea was 6.5 while for the 27 control cases that did show tachypnea it was 4.36. Accordingly, the writer feels that in our cardiac group (which has approximately the same age distribution), where no obvious respiratory, or painful somatic, or " nervous " (such as hyperthyroidism) etiological factors are present, it is permissible to assume that a

TABLE IIA

Organic Cardiac Cases Manifesting Tachypnea after Exercise
(24 plus/minute)

Case Key No.	Post-exercise Pulse/Respiratory Rate	Post-exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cardiothoracic Ratio)	Electrocardiographic Findings					Laboratory Pathology Factor and Remarks (LPF)
				Duration "P"	Duration "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Deviation	
Rm 7	132—24	5.5	13.2/28.6	.08	.16	.06	—	*Marked RAD*	LPF—I
Rm 38	132—24	5.5	13.8/30	.10	.20	.05	—	*RAD*	LPF—I
Rm 54	114—24	4.75	12.5/29.5	.08	.16	.06	—	—	LPF—0
Rm 60	114—24	4.75	12.5/29.5	*.08 Split P2 & P3*	.16	.07	—	*RAD*	LPF—II
Rm 65	174—24	7.33	10/28.5	.08	.16	.06	—	—	LPF—0
Ra & m 22	108—24	4.5*	*14.5/29*	.10	.20	.07	T_3 neg.	*Marked RAD*	LPF—II
Ra & m 24	126—24	5.25	13.9/31	.09	.16	.04	*T_1 flat. T_2 T_3 neg.*	—	LPF—I
Ra & m 25	168—24	7	13.3/30	.08	.16	.04	—	—	LPF—IV
Ra & m 28	108—24	4.5*	*16/30.5*	*.12*	.20	.07	*$T_{1, 2, 3}$ cove*	*LAD*	LPF—IV
Ra & m 30	114—30	Resting 3.9>3.8*	12.5/27.2	.09	.16	*.09*	—	LAD	LPF—II B.P. 202/130
Rm 32	138—24	Resting 6.44>5.75	*13.2/26*	.08	.16	.04	T_3 neg.	—	LPF—I
Rm 34	126—32	Resting 5.63>3.94*	*14/29.5 full left border*	.08	.16	.05	—	Slight RAD	LPF—I
Rm 37	162—30	5.4	12.9/29.5	*.15*	.20	*.14*	*T_2, T_3 neg.*	*RAD*	LPF—IV. Shows rt. bundle branch block
Ra 9	114—28	Resting 4 = 4*	15/31	.08	.16	.05	*T_1 neg.*	*LAD*	LPF—II
Ra 13	120—24	Resting 5 = 5	13.5/27.2	.08	.16	.06	—	—	LPF—0
Ra 15	144—24	6	13.5/30	.08	.16	.06	T_3 neg.	*RAD*	LPF—I

TABLE IIA—*Continued*

Case Key No.	Post-exercise Pulse/Respiratory Rate	Post-exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cardiothoracic Ratio)	Electrocardiographic Findings					Laboratory Pathology Factor and Remarks (LPF)
				Duration "P"	Duration "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Deviation	
M 12	138—24	Resting 6 > 5.75	11.8/28.6	.08	.17	.05	—	*RAD*	LPF—I
M 13	114—24	4.75	11.2/28.5	.08	.16	.06	—	*LAD*	LPF—I
M 16	144—24	6	13.6/32.5	.07	.16	.06	—	—	LPF—0
H 14	144—33 (after 26 hops.)	Resting 4.4 > 4.37*	13.9/32	*.14*	.20	.05	—	—	LPF—I B.P. 206/106
L 4	120—30	4*	*18/30*	.08	.16	.06	*T_1 neg.*	—	LPF—II B.P. 200/55
A 10	124—36	3.44*	13.5/32	*.12*	*.24*	.05	*Coronary T_3*	*LAD*	LPF—IV Low voltage
A 11	114—24	Resting 4.75 = 4.75	14/31.5	.08	.16	.08	*Flat T_1, Diphasic T_2, Neg. T_3*	—	LPF—I
A 12	96—24	4*	15/30.5	*.12*	*.24*	*.12*	*Coronary T_3*	*Poor EMF Notched QRS*	LPF—V
A 14	138—27	Resting 8 > 5.1	11.8/29	.10	.20	.06	*Flat T_1, T_2, T_3*	*RAD*	LPF—II
E 1	90—28	Resting 3.3 > 3.2*	12.5/28.5	.10	.16	.06	—	—	LPF—0; shows mod. cyanosis at rest
E 2	144—24	Resting 6 = 6	11.9/31	*.14*	*.24*	.08	—	—	LPF—II B.P. 198/118

KEY TO TABLE

1. Reduced pulse lability is indicated by star (*) after P/R ratio.
2. Paradoxical P/R ratio is indicated by resting being listed before post-exercise P/R ratio.
3. Definitely pathological laboratory findings are italicized. Thus each italicized item represents a "unit" of laboratory pathology.
4. The pathologico-anatomical diagnosis in each case may be ascertained by referring to the key letters listed in table 1.

pulse/respiratory ratio of similar reduced magnitude (i.e. 4.5 or less), is indicative of impaired cardiac function.

We shall now see how our laboratory studies checked up our clinical impressions. In this connection it is pertinent to emphasize that all the roentgen-ray and electrocardiographic readings were made by another physisian-specialist (Dr. R. S. E. Murray) who had no clinical contact with the patients, and so could not conceivably be influenced in interpreting the significance of doubtful or borderline plates or graphs. Before proceeding further we wish to mention all those laboratory findings which were considered definitely pathological. Roentgen-ray findings were considered definitely pathological only when the transverse diameter of the heart equalled or exceeded one-half the trans-thoracic diameter—except that three cases whose cardiac-thoracic ratio did not quite reach ½ (cases Ra and m 27, M 24, and Rm 34) were also considered definitely pathological because the roentgenogram revealed specific characteristic changes in the cardiac outline. The electrocardiographic findings which were considered as definitely pathological were classified under the following five headings: (1) P-wave changes—where the P-wave exceeded 0.10 second in duration; (2) P–R changes—where the P–R interval exceeded 0.20 second in duration; (3) QRS changes—where the *base* of the R-wave exceeded 0.08 second in duration; (4) T–wave changes—including negativity of the T–wave in one or more significant leads (not including an isolated T_3), as well as characteristic alterations in the T–wave configuration, such as coving; (5) definite axis deviations (marked ventricular preponderances), evidences of markedly increased or decreased voltage (only when extracardiac interfering factors were eliminated).

A perusal of the appended tables 2–A and 2–B, in which the definitely pathological laboratory findings are italicized, will clarify the above criteria. In order to arrive at a quantitative estimate of the sum of laboratory evidences of disease it was decided to count each group of significant findings, as arranged under the headings outlined in the preceding paragraph, as constituting a unit of laboratory evidence of disease. So that, the maximal index of laboratory evidence for any individual case would be six units (one roentgen-ray and five electrocardiographic units all indicating definite pathological readings). The unit score for each case we may term the "laboratory pathology factor" (L.P.F.) for that case; thus, case A–12 which shows the following definitely pathological laboratory findings: P equals 0.12 second; PR equals 0.24 second; QRS equals 0.12 second; coronary type T-waves; poor electromotive force has an L.P.F. of 5, while Case Ra and m 22 which has a cardio-thoracic ratio of 0.5 and a marked right ventricular preponderance as the only definitely pathological laboratory findings has an L.P.F. of 2.

TABLE II*B*

Organic Cardiac Cases *Not* Manifesting Tachypnea after Exercise

Case Key No.	Post-exercise Pulse/Respiratory Rate	Post-exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cm.) (Cardiothoracic Ratio)	(In Seconds) Electrocardiograph Findings					Laboratory Pathology Factor (LPF) and Remarks
				Duration "P"	Duration "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Deviation	
Rm 31	132—18	7.33	11.5/27	.08	.16	.05	—	—	LPF—0
Rm 39	120—18	6.66	13.7/30.5	*.14*	*.24*	.06	—	—	LPF—II
Rm 55	96—18	5.33	12/29.2	.08	.16	.08	—	—	LPF—0
Rm 58	96—20	4.8	12.7/29	.08	.16	.06	—	—	LPF—0
Rm 59	96—14	6.85*	None	.09	.18	.04	—	—	LPF—0
Rm 61	126—20	6.3	13.7/29.5	*.12*	.20	.06	—	Slight RAD	LPF—I
Rm 62	144—12	12	10.6/26.6	.07	.14	.07	—	Slight RAD	LPF—0
Rm 63	126—18	7	12/26.7	.10	*.24*	.08	—	—	LPF—I
Rm 64	102—22	4.64	12/27.2	.08	.16	.08	—	—	LPF—0
Rm 67	126—18	7	13.1/30.5	.08	.17	.07	T_3 neg.	LAD	LPF—I B.P. 196/125
Ra & m 23	96—15	6.4	13.8/28	.08	.17	.06	—	Slight LAD	LPF—0
Ra & m 26	144—20	Resting 7.2=7.2	14/29	*.12*	*.24*	.08	*T_1, T_3 flat, T_2 diphasic*	—	LPF—III
Ra & m 27	132—20	6.6	*14/29 full left border*	*.12*	.20	*.12*	T_1 diphasic	*RAD*	LPF—IV
Ra & m 32	126—12	10.5	*16/30*	.09	.18	.08	*T_2, T_3 neg.*	*LAD*	LPF—III B.P. 160/110
Ra & m 38	90—18	5	12.7/30.4	*.12*	.20	*.12*	*$T_{1, 2, 3}$ diphasic*	Slurred	LPF—III
Ra 14	102—22	4.6*	*13.2/27.5 conus arteriosus 7.5*	.10	.20	.06	—	—	LPF—I

TABLE II*B*—*Continued*

Case Key No.	Post-exercise Pulse/Respiratory Rate	Post-exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cm.) (Cardiothoracic Ratio)	(In Seconds) Electrocardiograph Findings					Laboratory Pathology Factor (LPF) and Remarks
				Duration "P"	Duration "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Deviation	
M 14	126—18	Resting 9>7	12/29.5	*.20*	*.24*	.08	—	*RAD*	LPF—III
M 15	120—20	6	None	.08	.15	.08	—	Slight RAD	LPF—0 Female Case
M 23	90—18	5	13.8/28.4	.08	.18	.05	T_3 flat	—	LPF—0
M 24	90—15	6	*12.8/27 straight left border*	.08	.16	.06	T_3 neg.	—	LPF—I
M 26	120—20	6	12/29.5	.10	.20	.04	—	*RAD*	LPF—I
H 40	102—14	7.3	13.8/31.2	.08	.16	*.10*	—	—	LPF—I B.P. 232/140
H 39	96—18	5.33	14.3/32	.08	.16	.06	—	—	LPF—0 B.P. 190/130
H 38	114—20	Resting 6.4>5.7	*16.4/30.6*	—	—	Slurred QRS 3	*T_1 neg.*	—	LPF—II B.P. 210/100
H 15	168—21	8	11.8/28.5	.10	.20	.07	Diphasic T_1	—	LPF—0 B.P. 224/114
L 6	108—15	7.2	*16/32*	.08	.16	.07	—	Slight RAD	LPF—I
L 7	108—20	5.4	11.7/25.5	.09	.20	.07	Diphasic T_3	—	LPF—0
A 8	126—12	10.5	13.8/28.5	*.12*	.20	.06	—	—	LPF—I
A 9	96—18	5.33	*15/28*	*.12*	.20	.06	—	*Very high voltage*	LPF—III

Key to Table: Same as for table 2*A*.

Table 3 summarizes the scores which were arrived at in the indicated manner for the various clinical functional groups of cases. It shows that the group of organic cardiac cases as a whole showed an average L.P.F. of 1.25. The group presenting an exercise tachypnea of 24 plus had an average

TABLE III

Complete Data Organic Cardiac Cases

Clinical Grouping	Total Number of Cases	Total Number of Laboratory Pathology Findings ("Unit")	Average Laboratory Pathology "Factor"	Number and Percentage of Cases with No Definite Pathological Laboratory Findings
With tachypnea (24 plus/per minute) after exercise	27	40	40/27—1.48	6—22*%
Without tachypnea	29	30	30/29—1.03	12—41.4%
With "paradoxical" P/R ratio	15	21	21/15—1.4	3—20%
Without paradoxical P/R ratio	41	49	49/41—1.2	15—36.6%
With reduced pulse lability (P/R less than 4.5)	10	23	23/10—2.3	1—10%
Without reduced pulse lability (P/R greater than 4.5)	46	47	47/46—1.02	17—37-%
Total organic cases	56	70	70/56—1.25	18—32*%

L.P.F. of 1.48, as compared with an average L.P.F. of 1.03 for the group not showing tachypnea after exercise. In other words the group with tachypnea, on the average showed 44 per cent more definite laboratory evidence of disease than the group without tachypnea. Similarly, the group with a paradoxical pulse-respiratory ratio showed on the average, 16⅔ per cent more definite laboratory evidence of disease than the group without a paradoxical pulse-respiratory ratio. Finally the group with a pathologically diminished pulse lability (pulse-respiratory ratio less than 4.5) showed on the average 125 per cent more laboratory evidence of disease than the corresponding group without a diminished pulse lability (pulse-respiratory ratio greater than 4.5).

The last column of table 3 indicates the reliability of using these clinical groupings in predicting the absence of laboratory findings of definite pathological significance. Thus the group without tachypnea showed an incidence of cases without pathologically significant laboratory findings that was 87 per cent greater than occurred in the group with tachypnea. Similarly the group without paradoxical pulse-respiratory ratio showed an incidence of " laboratory negative " cases 83 per cent higher than was found in the group exhibiting a paradoxical pulse-respiratory ratio. Finally in the group with-

out diminished pulse lability the incidence of "laboratory negative" cases was 270 per cent higher than in the group showing diminished pulse lability.

Table 5 suggests another interesting clinical hint, which however would require statistical confirmation from a much larger series of cases, before it could be considered firmly grounded. In this graphic table, the average post-exercise pulse rates for organic cardiac cases with similar degrees of severity of laboratory pathology are plotted. The dotted line indicates these averages in the cases manifesting tachypnea of 24 plus, and the dash line indicates these averages in the cases manifesting no tachypnea. The graph suggests that in cases with tachypnea, a relatively slow pulse rate is more indicative of a severe lesion, while in the cases without tachypnea the reverse holds true,—viz., a relatively fast pulse rate is more indicative of a severe lesion. One is tempted to surmise that the reason for this is that with the more severe grades of functional cardiac impairment there generally co-exists a relative prolongation of the systolic phase of the cardiac cycle, so that the organism can more readily respond to the increased oxygenation demands of exercise by a relative greater utilization of the respiratory adjustment. However, insufficient data were at hand to adequately test this supposition.

TABLE IV

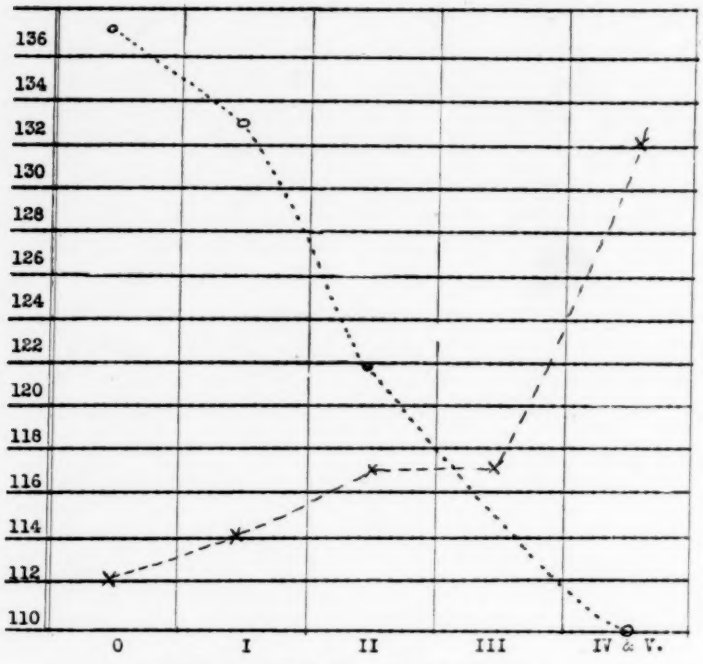
Comparison Roentgen-Ray Findings with Clinical Findings (Tachypnea) as to Sensitivity

Cases Showing	Number of Cases	Number of EKG.—L.P. "Units"	Average L.P. Factor for EKG. Findings —Alone	Number and Percentage of Cases with Negative EKG.
1. Roentgen-ray evidence of disease	12	13	1.08 plus	5—41 plus %
2. Tachypnea, 24 plus	27	35	1.3–	8—29.6 plus %
3. No tachypnea	29	23	.79 plus	15—51.6 plus %
4. Total organic cases	56	58	1.04–	23—41 plus %

Table 4 shows the relatively greater sensitivity of the simplest of these clinical criteria, viz., tachypnea, as compared with the commonly used laboratory criterion of pathological roentgen-ray findings. The electrocardiographic findings as expressed in laboratory factor averages are charted against these criteria. It seems clear that the presence of pathological roentgen-ray findings per se is no better indication of the presence of pathological EKG's than the diagnosis of organic heart disease per se. (Compare items (1) and (4) in the table.) On the other hand, the presence of tachypnea (after exercise) per se, affords a 20 per cent higher correlation with positive electrocardiographic findings, and a 25 per cent lower correlation with entirely negative electrocardiographic findings. (Compare items (1) and (2).)

TABLE V

Graph Indicating the Average Post-Exercise Pulse Rates for Groups of Cases with Identical Laboratory Pathology Factors (LPF).



SUMMARY

1. No entirely satisfactory clinical method has been available for the estimation of the degree of impairment of cardiac function in ambulatory organic cardiac cases.

2. Laboratory findings per se (roentgen-ray and electrocardiographic data) afford certain reliable *objective* criteria for the estimation of impairment of cardiac function in such cases.

3. This study of some 200 odd cardiac cases and 100 odd controls aims to determine the correlation existing between certain readily observable objective clinical data and the corresponding laboratory data. The tabular studies rather confirm the impression that a relatively high incidence of laboratory findings indicating functional impairment is found in those organic cardiac cases showing the following clinical signs:

(*a*) Tachypnea after exercise;
(*b*) " Paradoxical pulse/respiratory ratio " after exercise;
(*c*) " Diminished pulse lability " in response to exercise.

The definition of these terms is made clear in the text.

4. These studies were made on a clinical group of cases (mainly World War veterans) falling predominantly into certain age groups. Similar studies should be made on other more diverse age groups, before the conclusions arrived at can be considered generally firmly grounded.

5. The most tangible deduction from this study may be expressed in the following clinical aphorism: In an organic cardiac case manifesting tachypnea after exercise, a relatively slow pulse rate after exercise is more indicative of a severe lesion than a relatively fast one.

In closing it is pertinent to reëmphasize that these deductions and conclusions are considered to apply only to ambulatory organic cardiac cases, free of the influence of any drug therapy. Also that all the figures quoted represent averages, and so represent the usual tendency but not the invariable pattern of reaction of certain clinical groups of cardiac cases. In other words the clinical symptoms discussed, when present, may be considered as symptom-complexes suggestive of, but by no means pathognomonic of, the presence of impaired cardiac function. And conversely, the absence of these clinical symptoms may be considered as suggestive evidence, but again by no means conclusive evidence, of the absence of a significant impairment of cardiac function.

The author wishes to express his indebtedness to Dr. Reginald S. E. Murray of the Veterans' Facility, Lyons, N. J., as without his coöperation in furnishing extremely accurate and painstaking roentgen-ray and electrocardiographic reports, this study would have been impossible.

BLOOD VELOCITY RATE AND VENOUS PRESSURE IN THE PROGNOSIS OF HEART DISEASE *

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THE heart is well adapted to study because of its anatomical position and the numerous expressions of its activity. It may be easily observed as to size, shape, the state of its valves and the character of muscular contraction. Its situation in the thoracic cage, surrounded as it is by air-containing viscera, makes radiographic examination possible. By expelling its contents into a closed vascular system, it builds up the arterial, capillary and venous blood pressures and succeeds in imparting motion to a column of blood, i.e., velocity. The intermittent character of its contractions makes itself evident in a pulse wave and causes the propagation of minute electrical currents which may be registered graphically and interpreted. The accurate measurement of the various expressions of the physiologic activity of the heart enables us to assemble valuable information as to the state of the cardiovascular system.

Much has been written on blood velocity rate and venous pressure in heart disease. Most of the work has consisted of observations on patients during one short phase in their lives. It was therefore most natural that an attempt should be made to ascertain what changes took place in the hemodynamics of the circulatory system, when the disease process had an opportunity to regress or progress over a longer period of time. It was of particular interest to determine whether or not our studies could be of aid in prognosis.

Fifty-one cases of heart disease, rheumatic, arteriosclerotic and hypertensive, who were in-patients at the Jewish Hospital of Brooklyn, were studied. Forty-eight cases were traced one year later. Two were entirely lost. One was excluded because of the malignant nature of the disease. Of the 48, 17 were personally observed at the end of the test period. The remainder were followed through other institutions or through their family physicians.

The velocity rate (circulation time) was determined according to the method of Fishberg, Hitzig and King.[1] Saccharin was injected intravenously in the antecubital fossa and the time which elapsed between the injection and the patient's experiencing a sweet taste was measured. The normal rate ranges from 9 to 16 seconds.

Venous pressure was measured by the direct method of Taylor, Thomas and Schleiter who employed an ' L '-shaped tube which was connected with a needle placed in a vein under standard conditions.[2] The normal values are from 4 to 8 centimeters of blood.

* Received for publication October 8, 1936.
From the Medical Service of Dr. M. A. Rabinowitz, Jewish Hospital of Brooklyn, New York.

TABLE I

Patient No.	Diagnosis	C.T.	V.P.	$(V.P.)_2$	One Year Later		
					C.T.	V.P.	$(V.P.)_2$
		seconds					
1	Acute rheumatic fever; mitral regurgitation.	10.0	7.5	—	*		
2	Acute exacerbation of rheumatic fever; mitral regurgitation and stenosis; pericardial effusion.	10.0	10.5	10.5	18.0	5.0	5.0
3	Acute rheumatic fever; mitral regurgitation and stenosis; polyarthritis.	10.0 11.0	9.5 8.0	9.5 8.0	*		
4	Acute exacerbation of rheumatic fever; mitral and aortic regurgitation and stenosis; polyarthritis.	12.0 10.0	13.0 —	15.0 —	No Trace		
5	Acute exacerbation of rheumatic fever; mitral regurgitation and stenosis; pancarditis; aortic regurgitation; auricular fibrillation.	16.0 13.5 12.0 17.0 17.0	8.5 7.5 11.5 4.0 8.0	— 9.5 — 7.0 9.0	Died		
6	Subacute bacterial endocarditis.	15.0	10.0	10.0	Excluded (a)		—
7	Acute rheumatic polyarthritis; mitral stenosis.	19.0 21.0	6.0 9.5	— 9.5	17.0	3.5	3.5
8	Subacute polyarthritis; mitral regurgitation and stenosis.	15.0	8.0	8.0	*		
9	Acute exacerbation of rheumatic fever; pancarditis; pericardial effusion; rheumatic pneumonitis; mitral and aortic regurgitation and stenosis.	15.0 12.5 11.0 16.0 10.0	7.5 7.5 11.0 7.5 6.5	10.0 — 15.0 8.5 6.5	17.5	5.5	5.5
10	Chronic rheumatic valvular disease; mitral regurgitation and stenosis; C.P.C. of lungs, liver and extremities.	15.0	6.0	16.0	*		
11	Chronic rheumatic valvular disease; mitral and aortic regurgitation and stenosis; auricular fibrillation; C.P.C. of the lungs and liver.	30.0	12.0	19.0	Died		

TABLE I—*Continued*

Patient No.	Diagnosis	C.T.	V.P.	$(V.P.)_2$	One Year Later		
					C.T.	V.P.	$(V.P.)_2$
		seconds					
12	Chronic rheumatic valvular disease; mitral stenosis; auricular fibrillation; cardiac cirrhosis of the liver; ascites; umbilical hernia.	20.0 10.0 15.0	12.0 13.5 14.0	16.0 13.5 22.0	*		
13	Chronic rheumatic valvular disease; mitral and aortic regurgitation and stenosis; auricular fibrillation; cardiac cirrhosis of the liver; C.P.C. of lungs, liver and extremities.	29.0	22.0	30.0	28.0	18.5	—
14	Chronic rheumatic heart disease; mitral regurgitation and stenosis; C.P.C. of the lungs; coronary sclerosis; anginal syndrome.	26.0 15.0	7.5 7.0	8.5 9.0	Died		
15	Chronic rheumatic heart disease; mitral regurgitation and stenosis; C.P.C. of the lungs, liver; auricular fibrillation.	17.0	9.5	9.5	*		
16	Chronic rheumatic heart disease; acute exacerbation; mitral regurgitation and stenosis; C.P.C. of the lungs and liver; auricular fibrillation.	21.0 15.0 23.0 22.0 17.0	21.5 12.5 18.0 15.0 —	 15.5 20.0 20.0 —	*		
17	Chronic rheumatic heart disease; mitral regurgitation and stenosis; auricular fibrillation; embolization to extremities and mesenteric arteries.	31.0	11.0	11.0	Died		
18	Chronic rheumatic heart disease; mitral regurgitation and stenosis; C.P.C. of lungs, liver and extremities.	25.0 35.0	7.5 —	9.0 —	Died		
19	Chronic rheumatic heart disease; mitral regurgitation and stenosis; C.P.C. of the lungs; hyperthyroidism.	12.0	8.5	10.5	13.5	3.5	3.5
20	Chronic rheumatic heart disease; (lues); mitral regurgitation and stenosis; aortic insufficiency; auricular fibrillation.	19.0	9.5	8.5	*		
21	Chronic rheumatic heart disease; mitral regurgitation and stenosis; aortic regurgitation and stenosis; auricular fibrillation; decompensated	37.0 45.0	17.0 —	23.0 —	50.0 (b)	—	—

TABLE I—*Continued*

Patient No.	Diagnosis	C.T.	V.P.	$(V.P.)_2$	One Year Later		
					C.T.	V.P.	$(V.P.)_2$
		seconds					
22	Chronic rheumatic heart disease; mitral and aortic regurgitation and stenosis; auricular fibrillation; decompensated; hyperthyroidism.	55.0 45.0	17.0 15.0	23.0 23.5	* (c)		
23	Congenital heart disease; interventricular septum defect; decompensated.	17.0	15.0	18.0	12.0	11.0	15.0
	Arteriosclerotic Heart Disease						
24	Coronary sclerosis; myofibrosis cordis; anginal syndrome.	14.0 16.0	— 7.0	— 7.0	*		
25	Coronary sclerosis; anginal syndrome.	12.0	9.5	10.50	*		
26	Coronary sclerosis; acute coronary artery thrombosis.	17.0	8.5	9.5	20.0	2.5	3.0
27	Acute coronary artery thrombosis; generalized arteriosclerosis; diabetes mellitus.	13.5 17.0	5.5 7.0	— 7.0	*		
28	Coronary sclerosis; generalized arteriosclerosis; anginal syndrome.	20.0	18.0	18.0	18.0	4.0	6.0
29	Coronary sclerosis; myofibrosis cordis; anginal syndrome; diabetes mellitus.	25.0 22.0	6.0 9.5	8.0 10.0	*		
30	Coronary sclerosis; acute coronary thrombosis; ventricular aneurysm.	20.0 22.0	3.0 7.0	4.0 10.0	15.0	7.5	7.5
31	Coronary sclerosis; anginal syndrome.	19.5	15.5	—	15.0	8.0	8.5
32	Acute coronary artery occlusion.	21.0	6.5	6.5	Died		
33	Coronary sclerosis; diabetes mellitus; cystopyelitis.	17.0	12.0	12.0	*		
34	Acute coronary artery occlusion; coronary sclerosis; myofibrosis cordis; ventricular aneurysm; ventricular fibrillation.	20.0	—	—	Died		
35	Coronary sclerosis; myofibrosis cordis; congestive failure.	31.0 — 39.0	25.0 20.0 10.0	— — —	* (d)		

TABLE I—*Continued*

Patient No.	Diagnosis	C.T.	V.P.	$(V.P.)_2$	One Year Later		
					C.T.	V.P.	$(V.P.)_2$
		seconds					
36	Coronary sclerosis; congestive heart failure; anginal syndrome.	45.0 46.0	14.0	21.0	Died		
37	Coronary sclerosis; complete heart block; Stokes-Adams syndrome; decompensated.	25.0 28.0	16.5 —	— —	*		
38	Coronary sclerosis; generalized arteriosclerosis; myofibrosis cordis, decompensated with anasarca.	17.0 17.0 20.0	16.5 6.5 —	30.0 7.5 —	21.0	1.0	1.0
39	Coronary sclerosis; myofibrosis cordis; congestive heart failure; splenomegaly.	34.0 43.0 — 45.0	13.5 16.0 17.5 12.0	17.5 21.0 18.5 12.0	Died		
40	Acute coronary artery occlusion; coronary sclerosis; congestive heart failure.	35.0	12.0	17.0	Died		
41	Coronary artery disease; myofibrosis cordis; anginal syndrome.	31.0	9.0	—	Died		
	Hypertensive Heart Disease						
42	Hypertension; confluent bronchopneumonia; thrombosis of the leg; pulmonary infarct.	15.0	10.0	10.0	12.0	9.5	9.5
43	Hypertension; generalized arteriosclerosis; cardiac hypertrophy and dilatation; decompensated.	38.0	21.0	30.0	* (e)		
44	Hypertension; generalized arteriosclerosis; coronary sclerosis; lues; toxic thyroadenoma.	14.0	3.0	3.0	14.6	5.5	8.5
45	Essential hypertension; coronary sclerosis; auricular fibrillation; congestive heart failure; chronic cholecystitis.	23.0 30.0	9.5 8.5	12.0 13.0	13.0 (f)	4.0	11.0
46	Hypertension; generalized arteriosclerosis; cardiac hypertrophy and dilatation; decompensated; chronic nephritis; cerebral hemorrhage.	—	26.0	30.0	Died		
47	Essential hypertension; nephrosclerosis; asthmatic bronchitis.	14.0	8.0	—	30.0	21.0	28.0

TABLE I—*Continued*

Patient No.	Diagnosis	C.T.	V.P.	$(V.P.)_2$	One Year Later		
					C.T.	V.P.	$(V.P.)_2$
		seconds					
48	Hypertension and arteriosclerosis; coronary sclerosis; hypertensive retinopathy; chronic uremia.	15.0	7.0	7.0	No Trace		
49	Hypertension and arteriosclerosis; coronary sclerosis; myofibrosis cordis; myocardial failure; auricular fibrillation.	27.0 51.0 24.0	6.0 9.5 4.0	— 13.5 4.0	Died		
50	Hypertension and arteriosclerosis; coronary sclerosis; decompensated; auricular flutter.	42.0 34.0 35.0 20.0 20.0	30.0 21.5 14.0 14.5 15.0	30.0 30.0 — 21.0 16.0	(g) 27.0	28.0	30.0
51	Hypertension and arteriosclerosis; coronary sclerosis; decompensated; diabetes mellitus.	17.0	7.5	8.5	*		

C.T.—Circulation time in seconds.
V.P.—Venous pressure.
$(V.P.)_2$—Venous pressure after pressure over right upper quadrant.
* Patient living, traced through family physician or hospital.
(a) not included in statistical survey because of malignant nature of the disease.
(b), (c), (d), (e), (g), Velocity rate at first observation 30 seconds. At the end of one year functional capacity Class 3. Patient No. 50 died 20 months after first observation. Patient No. 21 died immediately post-thyroidectomy.
(f) Velocity rate at first observation 30 seconds. At the end of one year functional capacity Class 2*a*.

In arranging the tables which follow, in those cases on which more than one observation was made, the slowest velocity rate and the greatest venous pressure (not necessarily the coincidental one) were chosen. This was done because it was felt that these figures represented the greatest inefficiency which was registered by the particular circulatory system under study.

TABLE II

Circulation Time	Number of Cases	Number of Deaths in One Year	Mortality %
9–16 seconds	13	0	0
17–29 seconds	21	4	19%
30 seconds or more	14	8	57%

Case 50 is included in the preceding table, but it is not noted as a death. A total ablation of the thyroid gland was done 10 months after a circulation time of 42 seconds was recorded. The patient lived for another 10 months. Case 21 is also included in the above tables and is not listed as a death because death followed immediately after thyroidectomy. The operative procedure was done one year after the patient was first observed and was decided upon only after his decompensation failed to respond to any form of therapy. Cases 6 and 46 were excluded entirely. The first was one of subacute bacterial endocarditis; the second patient was semicomatose and the circulation time could not be obtained.

Berinskaya and Meerzon concluded that a marked slowing of the blood velocity had a bad prognostic significance.[3] Fishberg, Hitzig and King presented a study of 59 cases of recent myocardial infarction in the *Archives of Internal Medicine* of December 1934.[4] In 38 of these the circulation time was recorded. The following is adapted from table 3 of their article.

TABLE III

Circulation Time	Number of Cases	Number of Deaths	Mortality %
9–16¾ seconds	9	1	11%
17–29¾ seconds	15	2	13%
30	14	9	64%

(Adapted from Table 3 of article by Fishberg, Hitzig, and King.[4])

In both tables 2 and 3, it is evident that the mortality rate increases rapidly when the circulation time exceeds 30 seconds. The cases of Fishberg et al. were all of recent myocardial infarction and apparently were not followed up after the original investigation. It is probable that with a 12 month follow-up their markedly delayed velocity group would have presented much higher mortality rates.

In our mixed series, at the end of one year, there were six patients whose velocity rates exceeded 30 seconds and who were still alive. The importance of the finding of a very slow velocity rate is emphasized by the fact that of these six patients, five belonged to Class 3 and became decompensated on the slightest exertion. The sixth showed a remarkable improvement. At the end of the year his circulation time fell from 30 to 13 seconds. The following are synopses of the histories of these cases.

Case Reports

(*No. 22*) R. F., male, aged 45 years. Chronic rheumatic valvular heart disease; mitral regurgitation and stenosis; auricular fibrillation; congestive heart failure. On admission, there were dyspnea, cyanosis, râles at both bases, fluid in the pleural and abdominal cavities and a liver enlarged to the iliac crest. The circulation time was 55 seconds. The venous pressure was 17 centimeters, and it rose to 23 centimeters after right upper quadrant pressure. Since then, he has had repeated episodes of decompensation and is incapable of even the slightest exertion. Class 3.

(*No. 43*) I. L., female, aged 45 years. Hypertension, arteriosclerosis, cardiac hypertrophy and dilatation, decompensation. On examination, the patient was dyspneic, cyanotic and had sacral and pretibial edema. The heart was enlarged both to the right and left. There was an apical systolic murmur. The liver was enlarged to 8 centimeters' breadth below the costal edge. There was ascites. The eye-grounds showed arteriosclerotic blood vessel changes. The blood pressure was 230 mm. of mercury systolic and 124 diastolic. The circulation time was 38 seconds, the venous pressure was 21 centimeters. The patient decompensates very quickly and with little exertion. Class 3.

(*No. 50*) H. B., male, aged 53 years. Hypertension, generalized arteriosclerosis, coronary sclerosis, myofibrosis cordis, auricular flutter, congestive failure with enlarged liver, pulmonary stasis and peripheral edema. The blood pressure was 240 systolic and 120 diastolic. The circulation time was 42 seconds. The venous pressure was greater than 30 centimeters. The patient was readmitted twice within a period of nine months. The last circulation time was 27 seconds. On the third admission (10 months after the first observation) an ablation of the thyroid gland was done. It was most interesting to observe that, immediately following thyroidectomy, the heart rate changed from an auricular flutter to a regular sinus rhythm. Upon discharge the patient was still slightly decompensated. The circulation time was 27 seconds. The venous pressure was 19 centimeters. He was then admitted to an institution for chronic diseases. There he had several attacks of precordial pain and pulmonary edema. He made a sudden exitus 20 months after the first circulation time of 42 seconds was recorded. Class 3.

(*No. 35*) E. C., female, aged 55 years. Generalized arteriosclerosis, coronary sclerosis, myofibrosis cordis, anginal syndrome of nine years' duration, congestive heart failure with râles at both bases, a liver enlarged to 8 centimeters' breadth below the costal edge, and ankle edema. On admission the circulation time was 31 seconds. The venous pressure was 25 centimeters. Her family physician reported one year later that she was confined to bed for more than two-thirds of the time and that she decompensated with mild exertion. Class 3.

(*No. 21*) P. W., male, aged 44 years. Chronic rheumatic heart disease, mitral regurgitation and stenosis, aortic regurgitation and stenosis, auricular fibrillation, decompensated. On examination, there were orthopnea, cyanosis, fine crepitant râles at both bases and also large sonorous râles throughout the chest. The heart was enlarged to the right and left and the liver edge was felt at the level of the umbilicus.

On two separate occasions the circulation time was 37 seconds and 45 seconds. The venous pressure was 17 centimeters. After a month, he was discharged as improved. He was followed in the out-patient department where he always showed some evidence of decompensation. Eleven months after his first admission he returned to the hospital markedly decompensated. The circulation time was 50 seconds. There was a slight improvement after therapy and then a remission. A total ablation of the thyroid gland was decided upon. Unfortunately, the patient succumbed to the procedure. Class 3.

(*No. 45*) S. W., female, aged 48 years. Hypertension, generalized arteriosclerosis, coronary sclerosis, auricular fibrillation, anginal syndrome, congestive failure with enlarged liver. The circulation time was 30 seconds. The venous pressure was 9.5 centimeters and it rose to 12 centimeters after pressure was made over the liver area. In the year that followed she enjoyed fairly good health except for occasional precordial distress. When we observed this patient a year later there was no dyspnea or cyanosis. The lungs were clear. The apex beat was in the sixth interspace two inches outside the mid-clavicular line. She was fibrillating. Blood pressure was 190 systolic and 120 diastolic. The circulation time was 13 seconds. The venous pressure was 6 centimeters and rose to 13 centimeters after making abdominal pressure. Class 2A.

TABLE IV

Venous Pressure	Number of Cases	Number of Deaths in One Year	Mortality %
0– 8 centimeters	16	3	18.7%
9–19 centimeters	26	8	30.7%
20 centimeters or more	6	1	16.6%

It is evident that there is not the same progressive correlation between increasing mortality rate and increasing venous pressure that there is between mortality rate and increasing circulation time.

We were able to recall 17 patients at the end of one year. A complete physical examination and a determination of the circulation time and the venous pressure were done. The results are tabulated in columns 6, 7, 8, of table 1. Cases 2, 9, 47, 21, 45, and 50 were of unusual interest. The last three have already been discussed.

CASE REPORTS

(*No. 2*) D. S., female, aged 21 years. Acute exacerbation rheumatic fever, mitral regurgitation and stenosis, pericardial effusion. She suffered her first attack of rheumatic fever 14 years before her present admission. On examination she showed marked pallor, dyspnea, slight cyanosis and fever. There was dullness at both bases. The heart outline by percussion showed enlargement both to the right and left. The heart tones were muffled. There were presystolic and systolic apical murmurs and a pericardial friction rub. There was no peripheral edema and no enlargement of the liver or spleen. The circulation time was 10 seconds. The venous pressure was 10.5 centimeters. She made good progress and was discharged much improved.

One year later, she returned for an examination. She reported that she felt well on ordinary effort, but that she was no longer able to indulge in tennis or swimming without dyspnea whereas before her last illness she had experienced no difficulty in

these sports. Our physical examination showed no evidence of congestive failure. The heart was slightly enlarged to the left. There was an apical systolic murmur and an accentuated pulmonic second sound. Her circulation time was now 18 seconds, a marked increase over that of the preceding year. The venous pressure was 5 centimeters.

(*No. 47*) E. D., female, aged 44 years. Essential hypertension, nephrosclerosis, congestive heart failure. Her chief complaint was repeated attacks of whistling in the chest with shortness of breath. She appeared chronically ill. There were many musical wheezing râles, with the prolonged expiration, throughout the chest. There was an accentuated aortic second sound. The liver edge was palpable. There was no peripheral edema. She was tested in another clinic and found to be sensitive to feathers. There was much discussion as to whether the asthmatic attacks were allergic or due to heart failure. The circulation time was 14 seconds. The venous pressure was 8 centimeters. This, certainly, did not point toward the heart as being the seat of disease and responsible for the symptoms. In relation to this, we must call attention to the report of Winternitz on two cases of so-called "cardiac asthma" where the circulation time was normal.[10]

One year later she reported that after leaving the hospital she had been ill in bed for two months. She now showed a blood pressure of 220 systolic and 140 diastolic and a pulse rate of 96. The heart was enlarged to the right and left. There was an apical systolic murmur and an accentuated second aortic sound. There were no râles in the chest. The liver was palpated 4 centimeters below the costal edge. There was marked ankle edema. The circulation time was 30 seconds. The venous pressure was 21 centimeters and after right upper abdominal pressure it rose to 28 centimeters. There was no question now that there was myocardial insufficiency both from the physical examination and the determinations of the velocity rate of the blood and of the venous pressure.

(*No. 9*) S. L., male, aged 19 years. Acute exacerbation of rheumatic fever, pancarditis, pericardial effusion, rheumatic pneumonitis, mitral and aortic regurgitation and stenosis. On admission he showed dyspnea and cyanosis. There was dullness at both bases and evidence of a pericardial effusion. The liver was slightly enlarged. There was no peripheral edema. The problem which presented itself was whether or not this patient was suffering from myocardial failure with decompensation or whether the underlying process was purely a severe rheumatic infection. It was the prevailing opinion that we were dealing with an acute exacerbation of an old rheumatic heart disease. This was borne out by the therapeutic test when the patient failed to respond to digitalization and diuretics. Fever continued for weeks and subsided with the return of the physical findings to a more normal state. The circulation time varied from 14 to 16 seconds. The venous pressure averaged 7.5 to 11.0 cm. He showed marked improvement.

One year later he returned saying that he had been well and had been working as a salesman with no distress. Our findings at this time were that he had no dyspnea or cyanosis and no peripheral edema. There were no râles in the chest. The apex beat was found in the sixth interspace one inch outside of the mid-clavicular line. The circulation time was 17.5 seconds. The venous pressure was 5.5 centimeters.

Discussion

There appear in the literature two main theories as to the mechanism of heart failure. The first and oldest is the "back-pressure" hypothesis which stressed the concept that failure of any chamber resulted in a damming up of blood behind that chamber.[5] Thus, dyspnea on effort and pulmonary

edema were ascribed to failure of the left ventricle which resulted in pulmonary congestion. Cardiac insufficiency associated with passive congestion of the liver and peripheral edema was attributed to failure of the right ventricle. The second and later assumption placed emphasis on diminished cardiac output as the principal factor.[6] Proponents of this belief explained pulmonary edema as being due to a failure of the right ventricle while the responsibility for increased venous pressure with peripheral edema fell upon a failing left ventricle which was incompetent in propelling sufficient blood.

In his treatise on the failure of the circulation, Harrison says, "the theory of diminished cardiac output must be discarded, for this hypothesis fails to account for the symptoms, and measurements of the cardiac output have shown that heart failure may be associated with a normal output of the heart and that clinical improvement may be accompanied by a change in either direction or by no change of this function. . . . The back pressure theory on the other hand offers an acceptable explanation of dyspnea and edema formation, is compatible with the clinical and pathological findings, and is in accord with the 'law of the heart' and other fundamental physiological principles." [7]

The French school of medicine has been noted for adherence to the back pressure theory and for insistence on the distinction between left heart and right heart failure. To Corvisart, Beau and Potain, the only picture of heart failure was that which we know of as right heart insufficiency. Fraentzel, Meiklen, Vaquez, Frank and Lian recognized failure of the left ventricle as a distinct entity.[8]

Left ventricular failure is brought about by hypertension, aortic valvular disease and myocardial infarction involving particularly the left ventricle. The most prominent symptoms are dyspnea and substernal oppression on exertion, paroxysmal dyspnea and acute pulmonary edema. The underlying pathology is venous stasis affecting the pulmonary circuit.[8]

Pure right heart failure with congestion of the liver and peripheral edema is most commonly seen in association with chronic pulmonary disease, congenital heart affections, tricuspid lesions and lesions affecting the pulmonary artery.

Right heart failure may be engrafted upon a chronic failing left heart. Thus, right and left heart failure may and frequently do, coexist.

Mitral stenosis is peculiar in that it places a mechanical obstruction in the out-flow tract of the lesser circulation. Pulmonary congestion, therefore, in this instance, is not predicated upon the basis of left heart failure.

There is an interesting syndrome of heart failure first described by Bernheim at Nancy in 1910.[9] He observed a group of cases of congestive heart failure with (*a*) enlargement of the liver, (*b*) peripheral edema, (*c*) absence of râles in the lungs, (*d*) enlargement of the left ventricle. At autopsy he noted that the hypertrophy of the left ventricle was associated with a marked hypertrophy of the interventricular septum which encroached

upon the lumen of the right ventricle so that there existed virtually a functional stenosis of that chamber. The symptomatology and the physical findings can be explained only by back pressure due to stasis behind the right ventricle. It is possible, therefore, for right heart failure to precede left heart failure even though the underlying disease process is in the left ventricle.

Congestive heart failure with hepatomegaly and peripheral edema is always accompanied by an increase in venous pressure. We may therefore utilize the measurement of venous pressure as a criterion of the degree of right heart failure. A necessary corollary, therefore, is that the absence of increased venous pressure rules out right heart failure.

In cardiac failure there is a slowing of the speed of blood flow (velocity). Thus, if the circulation time (rate of blood flow) is measured and found to be slower than normal, and if, at the same time, the venous pressure is measured and found to be within normal limits, it may be concluded with reason that there exists an inefficiency of the left ventricle. There is, then, in the simultaneous determination of the circulation time and venous pressure, a method of distinguishing right from left heart failure.

We have found that there is no necessary parallel between the venous pressure (criterion of congestive heart failure) and the slowing of the blood velocity. In table 1, patients 12, 14, 35 and 39 show that in the same patient at different times in his clinical course, the rate of blood flow and the venous pressure varied markedly without showing any direct relationship to each other. In other patients we have observed very slow velocity rates with absolutely no sign of congestive failure as in patients 17, 29, and 41. Fishberg et al. have demonstrated that there may be a normal or subnormal venous pressure in isolated failure of the left ventricle although there is a marked slowing of the circulation time.

It is obvious then, since the mortality rate varies directly with the circulation time and not with the venous pressure (venous pressure = index of right heart failure), that the mortality rate is dependent upon the efficiency of the left ventricle. Hence, left ventricular failure is of graver import than right ventricular failure.

Increased venous pressure can be detected without difficulty by simple physical examination. However, the circulation time can be determined only by some special procedure of which, fortunately, there are several simple ones.[1, 11]

Since the mortality rate varies rather regularly with the blood velocity, it is clearly evident in the determination of the circulation time, there exists a real adjunct in the prognosis of heart disease.

The determination of the blood velocity has also been found useful:

(1) In differentiating dyspnea due to myocardial failure from that of bronchial asthma, cerebral and pulmonary dyspnea.[10]

(2) In determining whether or not an anginal syndrome is associated with the presence of myocardial damage.[10]

(3) In separating ascites and edema of cardiac from that of extra-cardiac origin.[10]

(4) In uncovering a masked hyperthyroidism in the face of heart failure.[10, 11, 12]

In passing we must mention that Fishberg and his co-workers have practised making pressure on the liver while obtaining the venous pressure. This was done routinely in all of our cases. We too, have found that making pressure over the right upper quadrant of the abdomen while the manometer is in the antecubital vein is of aid in determining whether or not a hepatomegaly is due to venous engorgement. In 19 cases, where there was no congestive heart failure, the average rise in venous pressure on squeezing the liver area was 0.5 centimeters. In 23 cases, where congestive heart failure with an enlarged liver was present, the average rise was 5.6 centimeters, and varied from 2 to more than 14 centimeters.

Conclusion

In a series of 51 cases of rheumatic, arteriosclerotic and hypertensive heart disease, 48 of which were traced for at least one year, we have found that:

1. The circulation time is of greater significance in prognosis than the venous pressure.

2. The mortality rate increases as the velocity of the blood flow decreases and that when the circulation time is 30 seconds or more, the mortality rate is 57 per cent for one year.

3. Of the six patients with a circulation time greater than 30 seconds and alive at the end of a year, five were in Class 3 and decompensated with the slightest effort. The sixth patient improved clinically and the velocity rate fell from 30 to 13 seconds.

4. Failure of the left ventricle is of graver import than failure of the right ventricle.

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THE COMPLICATIONS AND HAZARDS OF FEVER THERAPY: ANALYSIS OF 1000 CONSECUTIVE FEVER TREATMENTS WITH THE KETTERING HYPERTHERM *

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The beneficial effect of intercurrent infection upon patients with chronic disease was noted many years ago and naturally suggested the therapeutic value of elevated body temperatures. The feasibility of such a form of nonspecific treatment was tested with tuberculin shortly after its introduction about 50 years ago. This was the first of a long series of suggestions for therapeutic fever production which have included the utilization of febrile diseases, protein fevers and numerous mechanical and electrical devices. Despite the large number of methods which have been recommended and are available, the end is not yet in sight, and scarcely a month passes without the proposal of a new device or a further refinement of an old method. This interest and activity is encouraging, for all of the available methods seem to have disadvantages, and the completely ideal procedure for therapeutic fever production still remains to be developed.

From the standpoint of therapeutic results the least common denominator of all methods seems to be the type of fever which is produced. Sweeping aside all arguments as to technic, the method of choice depends upon the ease and certainty with which a desired level of fever can be reached and maintained, the expense involved, the familiarity of the operator with the method, and, most important of all, the safety and comfort of the patient.

Because certain complications and hazards encountered in fever therapy depend entirely upon the height and duration of fever regardless of the method of production, we feel justified in presenting our observations of 1000 consecutive fever treatments given with the Kettering Hypertherm at City Hospital, Cleveland, Ohio from March 1934 to January 1936. The therapeutic results will not be discussed at this time.

The influence of higher fevers and longer treatments in increasing the hazards to the patient can be demonstrated because the treatments comprising this series fall into two distinct groups. The largest group consists of 830 treatments, during which fever of 103° F. to 105° F. was maintained for periods of 3 to 5 hours. These treatments were given to patients with acute and chronic arthritis, syphilis and various other diseases. The second group consists of 170 treatments, during which fevers of 106° F. to 107° F. were maintained for periods of 4 to 7 hours in patients with gonorrhea and its

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complications. For the sake of convenience, fevers of 103° F. to 105° F. will be referred to as mild treatments, and fevers of 106° F. to 107° F. will be referred to as severe treatments throughout the remainder of this paper.

No attempt is made to compare the complications and hazards observed in this series with those reported by other workers. We believe that most of the phenomena described here may be seen in any series of induced fevers of comparable elevations and duration except those, such as skin burns, which occur only when external heat is applied to the patient. Complications such as severe debility due to an induced disease like malaria, or the increasing difficulty in producing successive fevers, as in protein therapy, are lacking in this series.

Some comprehension of the method used is necessary for an understanding of the problems encountered in this series. The apparatus consists of a cabinet large enough to accommodate comfortably the body of a man in a prone position with his head outside. The cabinet is provided with a large sliding door on each side to allow for the taking of rectal temperatures, the periodic examination of the patient's skin and the arranging of blankets as necessary. Fever is produced by passing heated and humidified air over the patient's body. A separate compartment at the foot of the cabinet contains an electrical resistance coil heating element which heats the air, and a blower which causes it to circulate through the cabinet. A second heating element produces humidity by boiling water. Automatic controls maintain air temperature and humidity at the desired levels.

The patient arrives at the treatment room about 8 o'clock in the morning after a light breakfast or in a fasting state. After recording the temperature, pulse, blood pressure and weight, the patient is placed in the cabinet and all covering is removed. The air temperature of the cabinet, which is about 125° F. at the start of the treatment, is raised as rapidly as possible to 150° F. or 160° F. and the humidity is kept between 30 and 40 per cent. This preliminary period, during which the patient's temperature becomes elevated to the desired level, varies from one-half to two hours, but this time is not included in recording the duration of the treatment. When the desired degree of fever is attained, the body is covered with a light blanket, an electric fan is directed on the face, iced water or 0.6 per cent saline is given as desired and ice is rubbed on the face. At this time the temperature and humidity of the air in the cabinet are adjusted to the lowest level at which the desired body temperature can be maintained. When the treatment is finished the patient is removed from the cabinet, and the temperature falls in an hour or so to the pre-treatment level. After a bath the patient is sent to the ward or allowed to go home.

This study deals with 1000 consecutive fever treatments divided as mentioned above, into 830 mild treatments and 170 severe treatments. The mild treatments were given to 142 patients of whom 62 had chronic arthritis, 21 had acute arthritis, 9 had rheumatic fever or chorea, 15 had syphilis and

35 had a variety of conditions. The patients with chronic arthritis had treatments at 103° F. to 104° F. for three to four hours, the others usually had 105° F. for five hours. The number of treatments per patient averaged 5.8, but varied from one treatment in 28 patients to 23 treatments in one patient. The severe treatments were given to 62 patients with gonorrhea, either genital or metastatic. An attempt was made to treat these patients at as near 107° F. as seemed consistent with safety, and this temperature was maintained in each treatment at least five hours, and preferably seven hours. Many of the patients in the first group who received mild treatments were debilitated, undernourished and aged beyond their years, while those in the second group who received severe treatments were young, robust and in excellent general health. Despite the marked difference in physical condition of the two groups, only 39, or 4.7 per cent, of the mild treatments had to be discontinued, compared to 24, or 14.1 per cent, of the severe treatments. Of the 39 mild treatments which were discontinued, 21 were discontinued because of insistence on the part of the patient, lack of coöperation or delirium, five because of blisters or burns, eight because of diarrhea or persistent vomiting, three because of shock and two because of tetany. Of the 24 severe treatments, 12 were discontinued because of insistence on the part of the patient, lack of coöperation or delirium, seven because of blisters or burns, two because of diarrhea or intestinal cramps and three because of shock. When these figures are arranged in parallel columns and reduced to percentages of treatments given, the difference between mild and severe treatments becomes apparent.

Our plan to weigh patients routinely before treatment and again prior to their discharge from the department was seriously disrupted because of the difficulty of getting them upon the scales. This was the case in arthritics with painful or disabling disease and in all patients with severe nausea or debility following treatment. The observed changes in weight during therapy were closely related to the amount of fluid ingested and to vomiting. We have data on 172 mild treatments. In 67 instances the weight after treatment was within one pound of the pre-treatment level. This was considered no change. In 19 instances there was a gain in weight which varied from one to six pounds, while in 86 instances there was a loss. In nine treatments the loss was less than three pounds, in 29 treatments it was three to five pounds and in 27 treatments it was five to seven pounds. In 21 treatments weight loss varied from seven to 15 pounds. Of these 21 treatments, 19 were given to three patients. Excessive weight loss occurred repeatedly in successive treatments of the same patients who took fluids poorly and vomited repeatedly. In 18 severe treatments, weight was unchanged in eight, there was a gain in five and a loss in five, never more than 6 pounds. The weight changes observed in fever treatments are temporary as restoration to pre-treatment weight takes place within 48 hours in most instances.

Nausea or vomiting is a frequent source of discomfort. Patients often

feel nauseated or vomit once or twice during the treatment but this occurs most often in the rest period following the treatment, particularly in patients who must get up and dress to go home. In rare instances, vomiting occurs with sufficient severity during the course of the treatment to necessitate its premature termination. Nausea or vomiting was observed in 28.1 per cent of the 830 mild treatments or 233 times, and in 35.5 per cent of the 170 severe treatments or 57 times. The patients who received repeated treatments were studied to determine if the incidence of nausea or vomiting increased with successive treatments and whether or not there was an individual susceptibility to nausea or vomiting. Of 114 patients who received two or more mild treatments, 45 had nausea or vomiting. These patients received 399 treatments, and nausea or vomiting occurred in 52 per cent or 207 times. Of 37 patients who received two or more severe treatments, 10 had nausea or vomiting. These patients received 67 treatments, and nausea or vomiting occurred in 55 per cent or 37 times. Thus it is seen that the vomiting patients receiving several treatments had this symptom in 52 per cent and 55 per cent of their treatments compared to 28.1 per cent and 33.5 per cent of the whole group. Some patients escape nausea entirely, even on repeated treatments, while patients with nausea receiving several treatments have a higher treatment incidence than the whole group.

It was thought that the use of morphine increased the incidence of these gastric disturbances, but the figures do not substantiate this view. In 830 mild treatments, morphine was administered 672 times or in 80.9 per cent of the treatments. Of the 399 treatments given to 45 patients who developed nausea, morphine was administered 307 times or in 77 per cent. In the 170 severe treatments, morphine was administered 145 times or in 85.3 per cent. Of the 67 severe treatments given to 10 patients who developed nausea, morphine was administered 52 times or in 74.6 per cent. When possible morphine was withheld on succeeding treatments of those patients who were nauseated or had vomited previously. Although these figures seem to indicate that morphine played little or no part in the causation of vomiting several individual patients escaped vomiting when morphine was omitted.

The effect of fever therapy in causing anorexia was observed by noting the first regular meal which the patient was able to eat after treatment. In 188 mild treatments the patient was able to eat supper on the day of treatment in 35 instances or in 18.6 per cent (no anorexia). He was able to eat breakfast the next morning in 123 instances or 65.4 per cent (anorexia for 12 to 18 hours), and he was unable to eat until the following noon in 30 instances or 16 per cent (anorexia for 18 to 24 hours). Of 56 severe treatments the patient ate his supper on the day of treatment in 20 instances or 35.7 per cent (no anorexia), breakfast next day was the first meal in 25 instances or 44.6 per cent (anorexia for 12 to 18 hours), and he was unable to eat until the following noon in 11 instances or 19.7 per cent (anorexia for 18 to 24 hours). This disparity between the two groups is remarkable, espe-

cially when one considers that the severe treatments were not terminated until later in the day, usually from three to five hours nearer supper time, than were the mild treatments. This is a further indication of the vigor and robustness of the patients treated for gonorrhea and the weakness and debility of the other group. Inasmuch as patients miss breakfast and lunch on the day of treatment prolonged anorexia is undesirable, especially in debilitated patients.

Burns which necessitate terminating fever treatments constitute but a small proportion of the burns produced. In most instances the burns are blisters of small size and heal without scar formation, although second degree burns have been seen. Patients are warned of this danger of burns and even of scars, particularly when severe treatments are contemplated, and therapy is not discontinued because of this unless it seems likely that burns will be severe. They occur only on the ventral surface of the body and are most frequently seen over bony prominences, in scars, on pendulous breasts or on those other portions of the skin which Bierman has shown to be relatively intolerant of heat. In 830 mild treatments, burns were observed in 18 instances or 2.2 per cent. In 170 severe treatments, however, burns were seen in 23 instances or 13.5 per cent. It must be remembered that these thermal injuries to the skin result from hot and humid air alone, for the fever cabinet is so constructed that the patient's skin cannot come in contact with a heating element.

Tetany was occasionally seen, but only two treatments were interrupted because of it. Many mild instances probably occurred for patients occasionally complained of muscle cramps or stiffness of the hands. This is usually seen early in the treatment as the body temperature is rising and before morphine is given. The symptoms are fleeting, usually promptly relieved by lowering the cabinet temperature temporarily, the administration of morphine or of calcium gluconate intravenously. The tetany which occurs during fever treatments is due to alkalosis caused by the hyperventilation resulting from the respiratory stimulus of hot air to the skin. No alteration in calcium metabolism occurs, and because tetany develops early in the treatment, it is probably not related to chlorine metabolism. Morphine, because of its effect in depressing respiration, seems the ideal preventative. We have not noted undue cyanosis from its use.

Herpes labialis occurred in 45 of the 142 patients given mild treatments, or 31.7 per cent, and in 19 of the 62 patients given severe treatments or 30.6 per cent. The figures are given in relation to the number of patients, rather than the number of treatments, because this complication occurs but once in an individual patient during any continuous series of treatments. On one or two occasions herpes labialis followed the second treatment only, but otherwise they were seen only after the first treatment. A second attack has been observed once in a patient whose last previous treatment was given more than three months earlier. Herpes labialis appears three to five days

after the first treatment, remains five days and heals without leaving a scar. The lesions may be very extensive, covering the lower half of the face including the external and internal nares and involving the buccal mucosa.

The rarest accident in our experience, but by far the most alarming, and the one which constitutes the greatest hazard in fever therapy, is the occurrence of sudden and uncontrolled hyperpyrexia associated with mania and followed by deep coma, circulatory collapse and other symptoms closely resembling those of shock. This condition was seen three times in each group with an incidence in the mild and severe treatments respectively of 0.36 per cent and 1.76 per cent. In the three instances occurring during mild treatments the uncontrolled temperature rise was moderate, the collapse was less profound, and recovery was more prompt than in the cases with severe treatments. The affected patients receiving mild treatments had repeated subsequent treatments without untoward results. The sequence of events as they occurred in a patient who was being treated for gonorrhea was as follows: the patient's temperature had been between 106.8° F. and 107.2° F. for 40 minutes when muscular twitchings were noted, his temperature rose to 107.8° F. in five minutes despite the fact that both cabinet doors had been opened. He was removed from the cabinet promptly, an electric fan was directed upon his body and he was kept wet with tepid water. His temperature continued to rise, he was pulseless, his lips were pale, and he was in deep coma. His heart sounds were inaudible, and he had an involuntary bowel movement. After adrenalin was given intramuscularly, his heart sounds became audible, the heart rate was 200, but no peripheral pulse could be felt. His temperature reached 109° F. He was given 50 c.c. of 50 per cent glucose solution intravenously. A half hour later his pulse improved, the blood pressure rose to 78 over 50, the temperature fell to 107°, he recovered from his coma but was completely disoriented. After another half hour his temperature was 104°, he became oriented, and suddenly had copious projectile vomiting, severe abdominal cramps and a rigid abdomen. The vomiting and rigid abdomen persisted for about 72 hours. He was observed closely as a patient with suspected intestinal obstruction, but he made an uneventful recovery without operation. Another patient, treated for gonorrhea, started with mania followed by deep coma and circulatory collapse. He had a severe epileptiform seizure lasting about five minutes. Upon recovery he was found to have right facial paralysis and aphasia, both of which symptoms disappeared within about 10 days. It is such experiences, rare though they be, which remind us of the seriousness of fever therapy at high temperature levels.

SUMMARY

Attempts at artificial fever production for the past 50 years have resulted in the development of many successful methods based upon various principles. The complications and hazards of fever therapy depend primarily upon the height and duration of the fever produced.

The complications and hazards observed in 1000 consecutive fever treatments given with the Kettering Hypertherm have been analyzed. Two types of treatment were given: (1) mild treatments, given chiefly to patients with various chronic diseases, limited to a body temperature of 105° F., and never maintained longer than five hours; and, (2) severe treatments, given to patients with gonorrhea, in which a body temperature of 106° F. to 107° F. was maintained for five to seven hours. The proportionate number of treatments which had to be discontinued, the incidence of skin burns produced, the incidence and severity of circulatory collapse were much greater in the severe treatments than they were in the mild treatments. The incidence of anorexia and excessive loss of weight after mild treatments was greater than after severe treatments. The incidence of herpes was unaffected by the severity of the treatments.

Despite the complications and hazards observed, the production of artificial therapeutic fever, with body temperatures even to 107° F. maintained for five hours or longer, under proper conditions of supervision has proved to be a practical and satisfactory procedure.

LIVER FUNCTION IN RHEUMATOID (CHRONIC INFECTIOUS) ARTHRITIS; PRELIMINARY REPORT *

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DURING the past few years, much interest has been focused on the subject of decreased dextrose tolerance in acute infectious diseases. Williams and Dick [1] found a decreased tolerance in 41 per cent of patients and they also found a similar disturbance in carbohydrate metabolism in experimentally induced toxemia in animals. Their paper contains an excellent review of the literature.

Two explanations have been offered for the "diabetic" type of dextrose tolerance curves obtained in these conditions. Some authors [1, 2, 3] ascribe it to lack of endogenous insulin caused by the functional impairment of the islets of Langerhans, while others [4, 5, 6] maintain that it is due to an interference with the action of the available insulin, whether of endogenous or exogenous origin. These interpretations are based upon the belief that the normal dextrose tolerance curve is dependent upon an increase in the circulating insulin consequent to pancreatic stimulation from the dextrose administered. However, Soskin et al.[7] have shown recently that a normal dextrose tolerance curve may be obtained in a completely depancreatized dog which is receiving an amount of insulin and dextrose just sufficient to maintain the blood sugar at a constant level. They also state [8] that "an animal in this condition shows a hypoglycemic reaction at least as great as that of a normal dog following the cessation of prolonged administration of dextrose." They reason, therefore, that the normal reactions to the administration of dextrose do not require the secretion of additional insulin and that the abnormal curves observed in toxemia do not result from the lack of extra secretion.

From the results of simultaneous observations on the sugar content of the blood entering and leaving the liver during tests for dextrose tolerance, they [7] concluded that "in the presence of a sufficiency of circulating insulin, but not necessarily of an extra secretion from the pancreas, the normal liver responds to administered dextrose by decreasing its own output of blood sugar which it previously had been supplying from its own resources." Their findings have been substantially confirmed by Tsai and Yi [9] who calculated the quantity of sugar entering and leaving the liver by means of a flowmeter. Soskin et al.[7, 8] then concluded from their experiments that

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the toxemia probably interferes with the homeostatic mechanism of the liver as postulated above, through its effect on the liver itself. Sweeney and his associates [5, 6] believe that the toxemia acts, not by suppressing the endogenous insulin supply, but rather by interfering with the function of insulin, whether of endogenous or exogenous origin. Yannet and Darrow [10] during the course of intoxication in rabbits produced by the intravenous injection of diphtheria toxin did not find any gross disturbance in carbohydrate oxidation. They did observe changes in the liver, however, and concluded that the observed changes in carbohydrate metabolism were due to a disturbance in hepatic function. Soskin et al.[11] found that the intravenous injection of diphtheria toxin into normal dogs caused a definitely prolonged dextrose tolerance curve, while the injection of boiled toxin was without effect. In depancreatized dogs, the curves after the injection of toxin were even more abnormal than in normal animals, although the preliminary curves were quite normal. They concluded, therefore, that abnormal dextrose tolerance occurring in cases of toxemia was due to the effects of the toxemia on the liver and not on the pancreas. This is not surprising when one considers that, incidental to its function of detoxication, the liver bears the brunt of the toxemia which accompanies acute or chronic infection. Because of these observations, a study was begun in 1932 to determine whether any disturbed liver function occurred during the toxemia of rheumatoid (chronic infectious) arthritis.

Patients were selected on admission to the clinic and divided into severe, moderately severe and mild rheumatoid arthritis. Only those patients with classical symptoms of rheumatoid arthritis were included in this study.

The Azorubin S test was selected for the liver function test. Tada and Nakashima [12] in a study of 62 dyes found that, while other dyes were excreted in large part by the kidneys as well as by the liver, 95 per cent of intravenously injected Azorubin S was eliminated by the liver and only 5 per cent by the kidneys. Using the duodenal tube, they found that in normal persons the dye appeared in the bile in 17 minutes. Weiss [13] concluded that this test seemed to measure the functional capacity of the liver quite as well as the Rosenthal test.

Technic of the Azorubin S Test

The duodenal tube is passed in the morning on a fasting stomach. When the tube reaches the duodenum and a yellowish-brown bile begins to flow, 4.0 c.c. of a 1.0 per cent solution of Azorubin S are injected intravenously. Five minutes after the injection of the dye, 40 c.c. of a 25 per cent magnesium sulphate solution are injected through the duodenal tube. In normal individuals a characteristic, deep red bile appears about 17 minutes after the injection of the dye.

From 15 to 30 minutes was accepted as the normal appearance time of the dye. Less than 15 minutes and more than 30 minutes indicated liver

dysfunction in proportion to the decreased or increased appearance time of the dye. The interpretation of liver dysfunction in patients with a decreased appearance time is based on the findings of Whipple, Peightal and Clark [14] who reported a hypersecretion of phenoltetrachlorphthalein with small doses of phosphorus which they attributed to the irritative effect of the phosphorus on the parenchyma of the liver. Soskin and Mirsky,[15] working with dogs in which liver damage had been produced by the intravenous injection of diphtheria toxin, found three different stages of dextrose tolerance depending upon the extent of liver damage. They concluded that Stage I (early liver damage) " is characterized by an early decline in the inhibitory effect exerted by the administered sugar so that the liver fails to decrease its own supply of blood sugar as rapidly as normal and a 'diabetic' type of tolerance curve results."

Analysis of 100 Cases

In four cases the appearance time was less than 10 minutes; in 32 it was 10 to 15 minutes; in 45, 15 to 30 minutes; in four, 30 to 35 minutes; in nine, 35 to 40 minutes; and in six, over 40 minutes. Of the entire number studied, 55 per cent showed some liver dysfunction. In 15 patients with osteo-arthritis, four (28 per cent) showed liver dysfunction, compared to 55 per cent with rheumatoid arthritis. However, the series of patients with osteo-arthritis is too small to permit definite conclusions. The following patients with rheumatoid arthritis showed liver dysfunction: 27 of 34 severe cases (73 per cent); 21 of 44 moderately severe cases (47.5 per cent); and seven of 22 mild cases (25.25 per cent).

From these figures it would appear that to some extent the liver dysfunction is parallel to the severity of the disease. There was no relation between the duration of the disease and the liver function. Although no control series is reported here, liver dysfunction in patients with severe rheumatoid arthritis is so much more frequent than in patients with mild rheumatoid arthritis (73 per cent compared to 25.25 per cent) that it suggests that liver dysfunction in such a high percentage is an abnormal finding. Cytological examinations of the bile in 50 cases showed abundant leukocytes in 24, or 48 per cent. Some patients with achlorhydria responded to stimulation with histamine or neutral red. Many of them showed an abnormal liver function test.

Serum Proteins

A quantitative determination of serum proteins was made in patients showing liver dysfunction. In most cases, there was a slight reduction of the total serum protein and a reversal of the albumin-globulin ratio. This occurred both in cases having a rapid dye appearance time and in those having a delayed appearance time. For example, in one case of rheumatoid arthritis the dye appeared in 37 minutes; the total serum proteins were 6.07

per cent; albumin, 3.5 per cent; globulin, 2.57 per cent; and the ratio, 1.36. In another case, the dye appeared in 12 minutes; the total serum proteins were 6.27 per cent; albumin, 3.81 per cent; globulin, 2.46 per cent; and the ratio, 1.55. A few cases with a normal Azorubin S test gave a reduction of the serum protein and a reversal of the albumin-globulin ratio. In the majority of cases studied, there was a correlation between liver dysfunction, the reduction of serum proteins and reversal of the albumin-globulin ratio.

Treatment of Liver Dysfunction

Where the bile showed an abundance of pus cells, cocci, etc., 10 c.c. of choleval were given intravenously twice weekly. Usually six to eight injections were given, depending upon the improvement of the cytology of the bile. When choleval was omitted, decholin-sodium was given intravenously in order to increase biliary drainage but, where a number of injections was given, a 5 per cent solution was used in order to prevent excessive secretion in those patients who may have had partial obstruction. This preparation has a tendency to increase biliary secretion and thus increase the elimination of detritus from the biliary tract.

Diet

The diet was regulated according to the requirements of each patient. In some patients with liver dysfunction, a high carbohydrate diet was given, and frequently there was a gain in weight and improvement in the constitutional symptoms. As far as could be ascertained, this did not produce harmful effects. This agrees with the recent reports of Bowen and Lockie.[16] A high protein diet was used in those patients showing nutritional edema. In view of the lowered values for serum proteins and the reversed albumin-globulin ratio in rheumatoid (chronic infectious) arthritis, noted previously by Davis[17] and confirmed by us, it is suggested that the diet be adjusted to conform with the requirements of each individual patient.

Discussion

A long series of papers has appeared on the relation of the liver function to plasma proteins. Kerr, Hurwitz and Whipple[18, 19, 20] noted a regeneration of serum proteins following a plasmapheresis, the globulin being replaced more rapidly than the albumin. They also noted that, after a 50 per cent depletion of serum proteins, regeneration took place in five to seven days. This is the time required for regeneration of the liver cells after hepatic necrosis produced by carbon tetrachloride. Recently, Whipple and his associates[21, 22] have given support to the theory that the liver is intimately concerned in the formation of serum proteins. The literature on the relation of hepatic disease to serum proteins has recently been reviewed by Snell.[23]

It has frequently been reported that, in advanced chronic hepatic disease, there is often a moderate reduction in the total serum protein. This reduction occurs mostly in the albumin fraction with reversal of the albumin-globulin ratio. In the less advanced cases albumin may be only moderately reduced but globulin may be increased. Rowe [24] believed that infection is probably responsible for these findings. Snell [23] concluded that "one of the fairly constant effects of parenchymatous hepatic disease is reduction in the serum albumin and reversal of the albumin-globulin ratio; that these changes are most probably related to deficient production of protein by the liver, and that for this reason they may have some diagnostic and prognostic significance; and finally, that the serum albumin is often at or near a level which makes the production of ascites and edema relatively easy." His work is in accord with that previously reported by Myers and Keefer.[25]

Davis [17] found a definite reduction in the serum albumin, a rise in the serum globulin, and a reversal of the albumin globulin ratio in all cases of severe rheumatoid arthritis. Although a greater change occurred in those cases classed as severe rheumatoid arthritis, less severe cases also showed some change. It is interesting to compare his findings in normal cases with his reports on one case of tumor of the liver, one of acute cholecystitis, and one of pernicious anemia, all of which may have had liver involvement. The mean findings in these three cases were: albumin, 4.05 per cent compared with 4.70 per cent in the normal group; globulin, 2.94 per cent compared with 2.26 per cent in the normal group; and the albumin-globulin ratio, 1.38 compared with 2.12 in the normal group. Although the degree of change was less, the findings in these three cases were similar to those observed in rheumatoid arthritis.

In view of the findings of Myers and Keefer [25] and Snell [23] of the reversal of the serum albumin-globulin ratio in liver disease, and of the present findings of liver dysfunction in 73 per cent of cases with severe rheumatoid arthritis, it is reasonable to assume that in most instances the changes in the serum proteins mentioned above and those also found by Davis [17] in rheumatoid arthritis may have been due to liver dysfunction.

Snell [23] stated that the principal effects referable to a reduced albumin content of the blood serum of patients with hepatic disease are related to the production of edema and ascites. He believed that, although the "edema level" (4 to 5 gm. per 100 c.c.) for the total serum proteins is not often reached, the disproportionate reduction in the serum albumin may reduce the osmotic pressure of the blood serum sufficiently to produce transudation, especially in regions where venous stasis occurs. Wells and his collaborators [26] have shown that, by direct measurement, the specific osmotic pressure of serum is a linear function of the concentration of albumin, the globulin content being relatively unimportant. It must be remembered, however, that there are other factors which may play a rôle in the causation of edema and ascites and that the lowered serum albumin may be only a contributing

factor. The above may offer some explanation for the edema found in some cases of rheumatoid arthritis and possibly for the many varied clinical syndromes appearing in this protean disease. It is also further suggestive evidence that rheumatoid arthritis is infectious in character.

Conclusions

1. Liver dysfunction, as determined by the rate of excretion of Azorubin S, was present in 55 per cent of 100 patients with rheumatoid (chronic infectious) arthritis.

2. Liver dysfunction occurred with greater frequency in patients with severe than in those with mild rheumatoid arthritis.

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A MEDICAL POET LAUREATE, ROBERT BRIDGES, M.D., POET LAUREATE OF ENGLAND 1913 TO 1930 *

By Commander Louis H. Roddis, F.A.C.P., *Medical Corps, United States Navy*

The Poet Laureate of England holds an official position of peculiar dignity and honor, even though the duties are nominal and the salary somewhat remarkable—a barrel of wine and one hundred and twenty pounds a year. The title is obtained from the laurel or bay, in classical times the crown of the hero and poet, the lover being crowned with myrtle. In 1921, Professor Broadus published a study of the office of the Poet Laureate, almost the first investigation of the subject made, and there still remains for some minor poet or literary historian, the pleasant task of writing the lives of the Laureates. The list, omitting some doubtful and "volunteer" Poet Laureates, includes but sixteen names and as a matter of interest they are here given:

Ben Jonson	Thomas Warton
John Dryden	Henry Pye
Thomas Shadwell	Robert Southey
Nathan Tate	William Wordsworth
Nicholas Rowe	Alfred, Lord Tennyson
Lawrence Eusden	Albert Austin
Colley Cibber	Robert Bridges
William Whitehead	John Masefield

Only one medical man has held the title, Robert Seymour Bridges, who was born at Walmer, Kent, England, October 23, 1844. His parents were in more than easy circumstances, and he was educated at Eaton and Oxford. His college was Corpus Christi, where he graduated B.A., with distinction, having still further distinguished himself as an oarsman. After a short period of travel on the continent he entered as a student at St. Bartholomew's Hospital from which he received his degree of M.B., in 1874, and where he served as house physician. Having completed his service he was appointed casualty physician at "Barts," as St. Bartholomew's has been known to generations of English physicians, and later was elected assistant physician to the Great Northern Hospital and to the Hospital for Sick Children in Grand Ormond Street.

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This is the ninth of a series of portraits of medical poets. Those which have previously appeared in the Annals of Internal Medicine are: Joseph Rodman Drake, February 1929; Oliver Wendell Holmes, June 1930; Oliver Goldsmith, May 1932; Wm. Savage Pitts, January 1933; Lieutenant Colonel John McCrae, June 1933; Dr. Richard Shuckburgh, June 1934; Johan Christoph Friedrich Schiller, March 1936.

In 1878 he published a paper in the St. Bartholomew's Hospital Notes, "An Account of the Casualty Department," in which he recorded his experiences as admitting physician. From nine o'clock until twelve noon he spent interviewing patients and sending them to the appropriate clinical outpatient departments for treatment. In a year he saw 30,000 patients, two-thirds of these new cases. His whole article gives a clear and striking picture of the casualty work of this great London Hospital more than half a century ago. He also contributed a report on a case of rheumatic fever, treated by splinting the affected joints with good results. His third contribution to literature was a semi-humorous poem of 558 lines, written in Latin and describing the foundation of St. Bartholomew's Hospital, with characterizations of its staff:

> "Carmen Elegiacum Roberti Bridges de Nosocomii
> Sancti Bartholomaei Londiniensi."

Such evidences of the classical learning of the author indicate how the medical tradition for classical scholarship established by Linacre, Caius and Heberden was carried on into the Victorian age.

Bridges had begun to write verse at an even earlier period, and his first volume of poetry appeared in 1873. From then until his death he continued to publish isolated verse, dramas, and successive volumes of poems. His last work, "The Testament of Beauty," appeared on his eighty-fifth birthday, so that his period of productive activity as a poet covered 56 years.

A number of physicians have distinguished themselves in art, literature and science, and still continued in the active practice of their profession. Medicine, however, is a jealous mistress, and many more have forsaken her to follow another love. This was the case with Bridges, and in 1882 he gave up his practice to devote himself more and more to poetry and scholarship. The possession of abundant private means enabled him to follow his inclinations in this respect without any difficulty. It is of interest to note that "Prometheus the Fire-Giver," one of the most ambitious of his earlier works, was published in 1883, the year after he had definitely abandoned Medicine.

To the end of his long life he remained a poet and scholar. Few other English poets have been such profound students of the art of versification or have admired, studied, experimented and exalted the use of English as a medium of expression. He was the author of a book on "Milton's Prosody," a penetrating study of rhythm and sound in English poetry. He was also one of the founders of the Society for Pure English and was the general editor of its publications. S.P.E. Tract No. 9 had as joint authors, Dr. Bridges and Dr. Cuthbert Morton. It was on the language of anatomy, so we see here his return to a medical theme. The object of the pamphlet was "to condemn the action of those who are moving to introduce a formal Latin international terminology into the British Schools of anatomy on the false note that it will be of service to international science." This was a plea

to use an English terminology. His last work, "The Testament of Beauty," is an attempt to introduce a radical change in English spelling. Indeed, Bridges was as distinguished in the field of English scholarship as he was as a poet. This preoccupation with scholarship, and what one might call the technical feature of versification, led to many of his poems giving an impression of careful design rather than spontaneous inspiration. This quality of his work is well shown in one of his most often quoted poems, "London Snows":

"When men were all asleep the snow came flying,
In large white flakes falling on the city down,
Stealthily and perpetually settling and loosely lying,
Hushing the traffic of the drowsy town;
Deadening, muffling, stifling, its murmurs failing;
Lazily and incessantly floating down and down."

Of the two eternal themes of the poets, Love and Nature, Bridges was concerned primarily with the latter. His love poems are few and justly criticized as lacking in passion and power. Some of these, however, are not lacking in a deep and simple tenderness, as in this:

"When death to either shall come,
I pray it be first to me,
Be happy as ever at home,
If so, as I wish, it be.

Possess thy heart, my own,
And sing to the child on thy knee,
Or read to thyself alone,
The songs that I made for thee.

Bridges has well carried on the tradition of English poetry as a mirror of the natural beauty of the English countryside, and has often in his verse celebrated:

"Fair England in Her Pastoral Dream."

Here is a stanza worthy of Spencer:

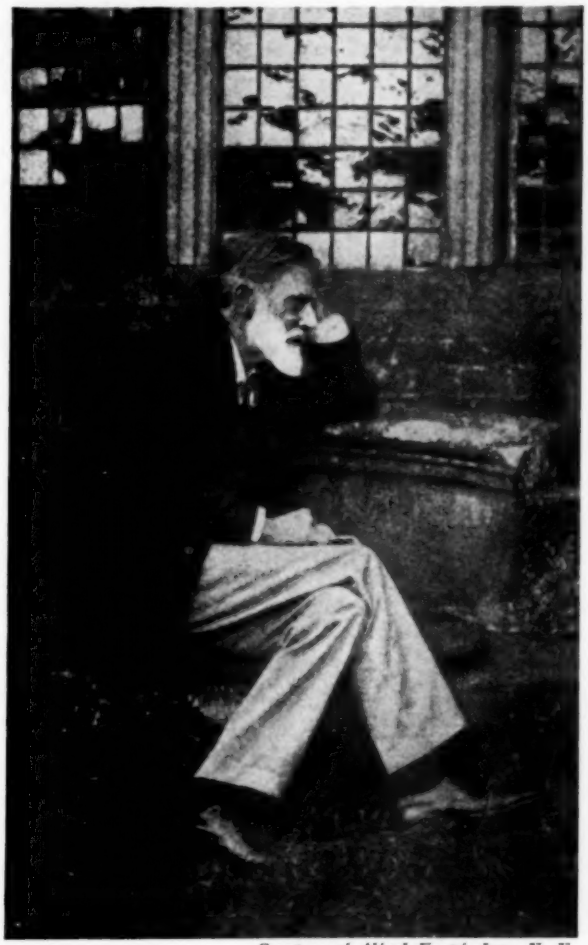
"There is a hill beside the silver Thames,
Shady with birch and brush and odorous pine;
And brilliant underfoot with thousand gems.
Steeply the thickets to his floods decline."

The flowers, beloved of all the poets, are often found in his verse:

"Pansy and Poppy-seed
Ripened and scattered well.

And silver Lady-smock
The meads with light to fill,
Cowslip and Buttercup,
Daisy and Daffodil."

The appointment of Bridges as Poet Laureate in 1913, as the successor of Alfred Austin, was a great surprise to many. Though recognized as a poet and scholar of high rank, he was not well known to the general public who would have welcomed some more popular poet, as Kipling or Alfred Noyes. Kipling at the time was the most famous, as he was the most



Courtesy of Alfred Knopf, Inc., N. Y.

ROBERT BRIDGES

national of the living English poets. None of the others had written one poem which all people knew, while he had written a dozen. It is said that he was not favored as a royal poet because of reference to Queen Victoria as the " Widow of Windsor."

The appointment, however, did not lead to as much criticism as was received by his predecessor in office. King Edward had a very poor opinion of the work of Alfred Austin, and in a letter to Lord Salisbury (quoted in

Sir Sidney Lee's Biography of Edward the Seventh) the King said, "I always thought that Mr. Austin's appointment was not a good one, but as long as he gets no pay it would, I think, be best, to renew the appointment in his favor." A little later he forwarded some of Austin's poetry to Salisbury and refers to it as "trash."

During the war there were remarks on the absence of war poetry on the part of the Laureate. He wrote, however, a number of war poems which were published anonymously. These were collected in 1920 in a volume entitled, "October and Other Poems." The supposed silence of the Laureate during the war led a Member in the House of Commons to inquire if the Poet Laureate should not be officially requested to "earn his butt of sack."

"The Testament of Beauty," Dr. Bridges' last work, was published on his 85th birthday and attracted more popular attention than any of his other poems. This was partly due to his adoption of simplified spelling. "There" became "ther," "captive" became "captiv," "will" became "wil." Silent letters are almost entirely dispensed with throughout the poem of 190 pages. It excited a great deal of controversy as do all such innovations, the more so that it was the work of the Poet Laureate and dedicated to the King. One line in it, "wher ther is any savagery; ther wil be war," was taken as an example of his simplified spelling and little was said in the press accounts and reviews of the poetical merit of the work.

Dr. Bridges received many honors other than that of Laureate. Oxford is only one of many universities that bestowed academic distinctions upon him. He was made Doctor of Laws and a Doctor of Literature. The Order of Merit, one of the most prized decorations, granted only for preeminence in art, literature, military affairs, and statesmanship, was bestowed upon him by the Sovereign. In 1920 he was elected to Fellowship in the Royal College of Physicians.

He died at his home, Chiswell House, Boars Hill, Oxford, April 21, 1930. He maintained the tradition of age among Poet Laureates by living for 85 years. His three predecessors were Austin, who died at 79 years, Tennyson at 81 years, and Wordsworth at 80 years; an average of 80 years.

There is an interesting story told of Bridges and his successor as Laureate. The doctor was fond of bicycling, and on one occasion he had a puncture in his front tire, on the slope of Boars Hill just at dusk, and was assisted in the repair of the tire by John Masefield.

Bridges was a handsome man and distinguished in appearance. He looked the part of a poet and a poet laureate. The portrait which illustrates this article shows him seated in his garden, a fitting picture as he was a lover of gardens and flowers and celebrated them repeatedly in his verse. Another well known picture of the poet shows him seated at a piano, presented to him by admirers on his eightieth birthday. Like so many poets and physicians he was an excellent amateur musician.

CASE REPORTS

"ABDOMINAL INTERMITTENT CLAUDICATION" AND NARROWING OF THE CELIAC AND MESENTERIC ARTERIES*

By William B. Seymour, M.D., and Averill A. Liebow, M.D.,
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Deprivation of the blood supply to the viscera is important among the causes of abdominal pain. The effects of sudden vascular occlusion are dramatic and well known. More obscure are the symptoms and pathology of gradual occlusion. Since the literature heretofore has treated these in a very stepmotherly fashion, the correlation of available clinical and pathological data may be of value.

Case Report

A spinster of 76 was admitted to the medical ward complaining chiefly of abdominal pain after eating. She had been in good health until about six months before admission. At this time she began to experience numbness in the left calf upon exertion, tingling sensations in the fingers, and constant tinnitus. The abdominal pain began three months before admission. Immediately upon the ingestion of any food except water and fruit juices there would appear a sharp steady pain in the region of the umbilicus radiating to the symphysis pubis, left lower quadrant and back. The pains would last 5 to 30 minutes and were followed by a constant slight dull ache in the epigastrium. On two occasions she had been nauseated and had vomited thin colorless material. One week before admission she had had a watery diarrhea of two days' duration. She thought that her stools had been black at times. There had been no abdominal distention. On account of the pain her diet had been entirely fluid and she had lost a considerable but indeterminate amount of weight.

Upon physical examination the weight loss was apparent in the dryness and looseness of the atrophic skin. Subcutaneous tissue was practically absent. The rectal temperature was 99.8° F., the pulse 72 and the respirations 18. There was marked evidence of arteriosclerosis: the retinal vessels were thickened and tortuous and the arteries of the extremities were firm cords. Pulsations were appreciable in the right femoral and dorsalis pedis arteries, absent in the left. In the right thigh the blood pressure was about the same as that in the right arm (200/80), but in the left thigh it could not be determined. This extremity was definitely cooler than the right. Its calf and thigh diameters were, however, the same as those of the right. The apex impulse of the heart was best palpated in the fifth intercostal space 7 cm. from the mid-sternal line. The rhythm was regular and the sounds were of fair quality with accentuation of the aortic second sound. A loud harsh systolic murmur was heard at the apex and a high pitched blowing diastolic at the base, most audible at the left sternal border. Examination of the chest revealed no evidence of pulmonary disease.

The abdominal wall was extremely lax. In the region between umbilicus and mid-epigastrium just to the left of the vertebral column most observers palpated a firm

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but vaguely defined, immovable, pulsating mass. No other masses were felt. There were no other notable findings in the physical examination.

Guaiac tests of the stools were positive on several occasions. No gross blood or "tarriness" was observed. The non-protein nitrogen of the blood was 39 mg.

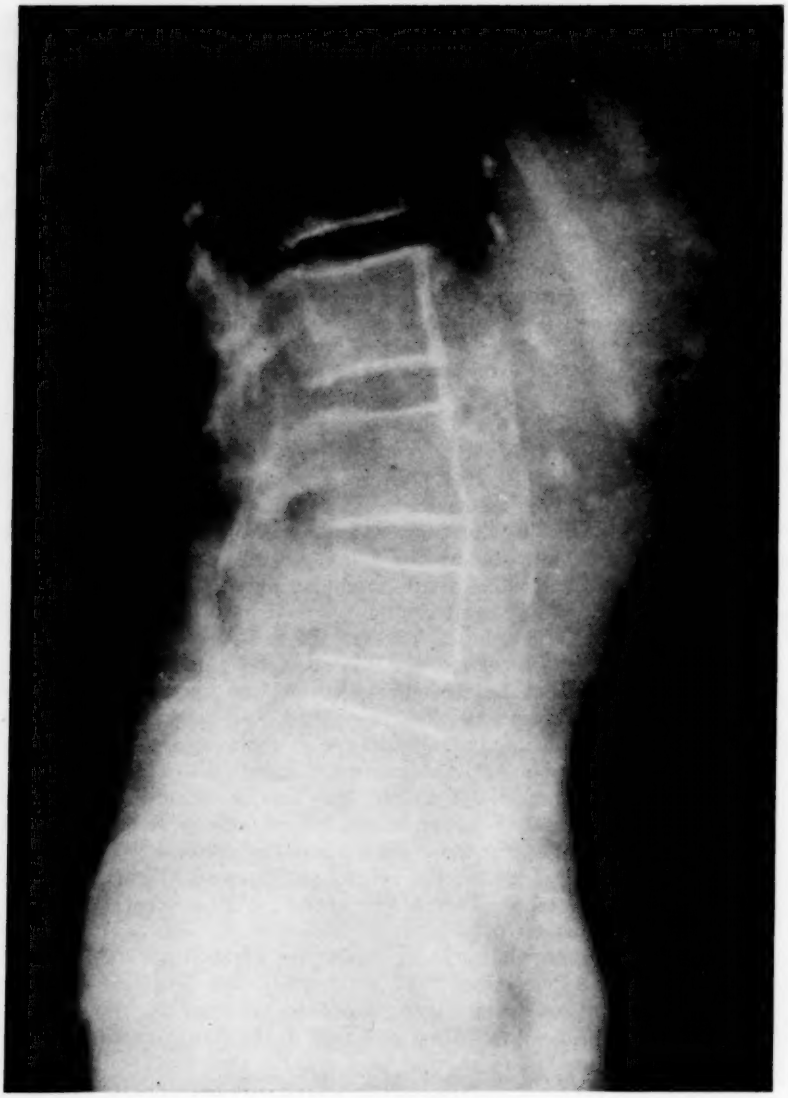

FIG. 1. Roentgenogram. Calcification of aorta.

per 100 c.c. The Kahn test was negative. The red blood cells numbered 4,300,000 per cubic millimeter with 90 per cent hemoglobin and the white blood cells 13,000 with 84 per cent polymorphonuclears, 14 per cent lymphocytes and 2 per cent L.M. The urine, except for the presence of 15 to 20 white blood cells in the low power field, was negative.

At this time the recorded diagnoses included generalized arteriosclerosis with hypertension, and occlusion of the left iliac artery. The pain and abdominal mass were variously interpreted as due to aortic aneurysm, carcinoma of the stomach, pancreas or intestine, or to mesenteric vascular occlusion. Roentgenographic examination demonstrated marked calcification of the abdominal aorta, and the gastrointestinal

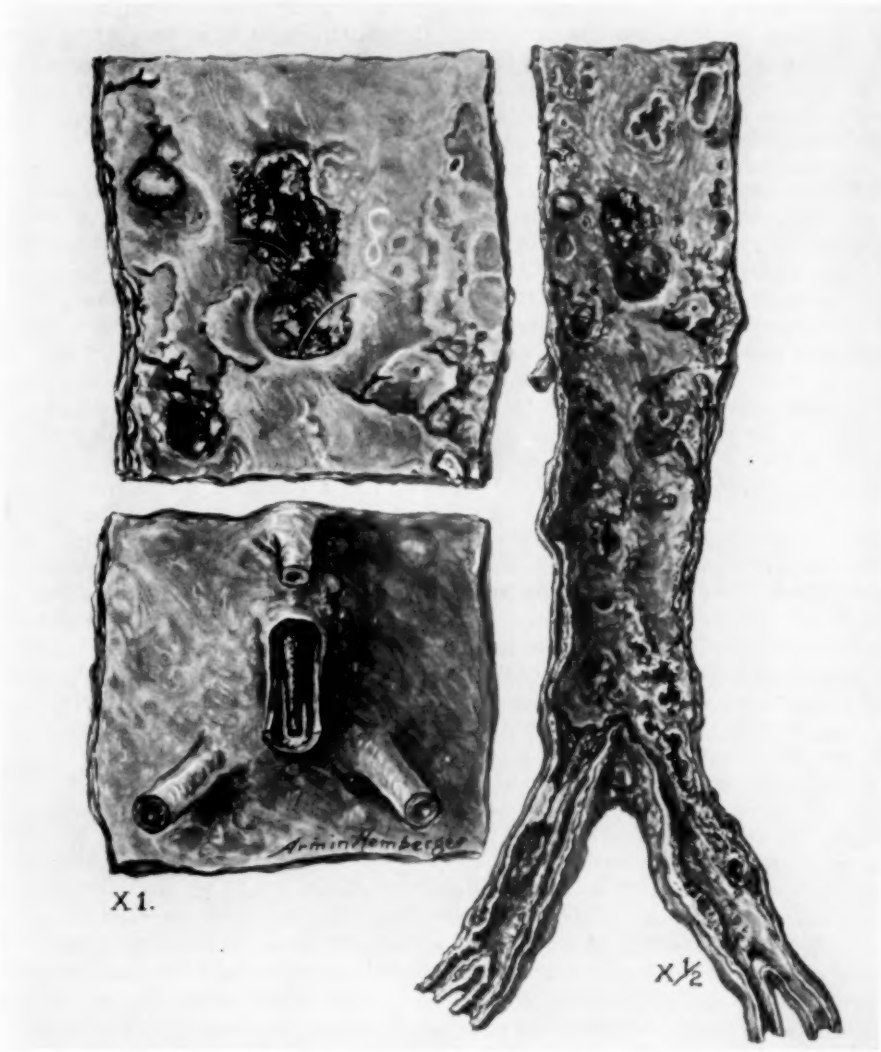

FIG. 2. Ulcerative atherosclerosis of aorta with obstruction of celiac axis, left iliac and mesenteric arteries; thrombi in superior mesenteric and left iliac arteries.

series revealed narrowing of the esophagus (interpreted as due to pressure of the aorta), atony of the stomach with 15 per cent retention of the gastric contents in six hours, and motor delay throughout the small intestine. Failure of the pylorus to dilate with peristalsis was thought compatible with the possible presence of a carcinoma in this region. Three stools in succession were guaiac positive. Nine days

after admission the patient vomited 300 c.c. of material resembling coffee grounds which was weakly positive for guaiac. These findings and the patient's great distress unrelieved by medical therapy induced the decision to perform an exploratory laparotomy.

At operation the peritoneal cavity was found to be devoid of exudate and the color of the intestines to be normal. On the lesser curvature of the stomach near the pylorus there was a tiny, firm zone slightly more vascular than the surrounding tissues to which the omentum was adherent. This was thought to be the serosal aspect of a small ulcer. The abdomen was then closed without further manipulation and the patient was returned to the ward in good condition. Soon thereafter, however, the blood pressure began to fall and the patient died 18 hours after operation despite supportive measures.

At postmortem, incision exposed dull, dark gray peritoneal surfaces. Fibrin covered the intestines, stomach and omentum, particularly at the site of operation. About 100 c.c. of foul dark purple fluid were collected in the right paracecal fossa and pelvis. The serous surfaces of the stomach and inferior surface of the liver were dull gray; those of the entire small intestine and proximal half of the large were dark purple. A loop of ileum adherent to the posterior wall of the bladder was almost black, and so soft that it tore easily in a gentle attempt to loosen the adhesion. The entire gastrointestinal tract was distended with dark red, malodorous fluid.

The mucosa of the stomach was gray, opaque and rugated in the usual fashion. Ulcerations were not found at any point and the vascular area observed at operation did not overlie any mucosal lesion. The pyloric layer of muscle was, however, unusually thick. Microscopic sections showed no evidence of carcinoma. Histologically the gastric mucosa was poorly preserved on account of postmortem change. The wall of the small intestine was so soft as to rupture readily in response to slight stress. A few small superficial ulcers were encountered in the lower ileum. Elsewhere in the ileum and in the large intestine the mucosal surface was opaque and gray-green but not ulcerated. The lower segments of the descending colon and sigmoid were of the usual appearance. The appendix was only 2 cm. in length and teat-like in shape. Its lumen was obliterated. Microscopically the mucosa of the small intestine had undergone complete necrosis. There was marked congestion of the vessels and hemorrhages were prominent at many levels. Cellular reaction was slight and of the polymorphonuclear type. Liver and pancreas grossly and histologically showed no evidence of infarction.

The aorta throughout its length was tile-hard and stiffly maintained its shape when placed upon the table. A remarkable gritty resistance was met in attempting to open the vessel from the rear. The intima in many places was raised by yellow, opaque atheromatous material. Elsewhere it had become superficially ulcerated or infiltrated with calcium now of oyster-shell consistency. About the mouth of the celiac axis was deposited a rosette of very hard material which virtually obliterated the ostium. Just distally, although thick-walled, the vessel was widely patent. The mouth of the superior mesenteric artery likewise was narrowed to an opening of pinpoint size by a hard incrustation in its wall. A firm, fresh, laminated, red and gray thrombus completely obstructed the proximal 5 cm. of the vessel. Its branches were dissected and found to be patent although thickened. The inferior mesenteric artery was firm-walled and neither increased nor decreased in caliber. The lumina of the left common and external iliac arteries were reduced to mere crescentic slits because of tremendous thickening of the intima. This consisted of eccentrically split laminae of hyaline connective tissue patchily infiltrated with calcium. Calcification of the irregular media was also prominent. A fresh thrombus partially occluded the left common iliac artery. The corresponding vessels on the right showed similar changes in lesser degree. Their lumina were not obstructed.

The heart weighed 313 gm. It had a deep fatty layer within which the coronaries were palpable as tortuous cords of wire-like firmness. Multiple sections showed marked encroachment upon the lumen by atheromatous plaques, many of which were calcified. Occlusion was at no point complete and no thrombi were found. Calcium containing, hyalinized intimal and medial plaques were demonstrated histologically to have reduced the lumina to narrow channels. In the deeper intimal and medial layers copper-brown refractile hemosiderin granules were evidence of organized hemorrhage. The myocardium, particularly that of the apex and roots of the papillary muscles, showed a moderate degree of fibrosis. There was no evidence of infarction. The aortic valve was slightly thicker than usual but not calcified. Its leaflets were movable and, as far as could be determined, capable of competent closure.

Summary of Case

In summary the history is that of a woman of 76 with marked evidence of arteriosclerosis who suffered from intermittent claudication in the left leg, and, latterly, with intermittent sharp abdominal pains coming immediately after eating. At postmortem there was found great narrowing of the left iliac vessels and of the celiac and mesenteric arteries at their mouths. Finally there was a recent thrombus in the last mentioned vessel with an infarct in the region of its distribution.

Discussion

The analogy which the recurrent abdominal pain bears with intermittent claudication in the extremities or with syphilitic or arteriosclerotic narrowing of the mouths of the coronary arteries with angina of effort is plain. The symptom of pain coming so soon after ingestion of food may be accounted for on the basis of the presumably markedly reduced blood supply to the stomach. Occlusion of the celiac axis in the presence of a normal superior mesenteric artery may be without clinical or anatomical result. Collateral circulation usually finds ready access from the superior mesenteric system through the pancreatico-duodenal loop.* Specific instances are presented by Thane and by Hecht. In the present instance, however, the mouth of the superior mesenteric artery was strikingly reduced in diameter by calcium concretions. In addition there was clinical evidence of early cardiac failure (slight edema, breathlessness). These factors tend to reduce the efficiency of a possible collateral blood supply. The exact mechanism responsible for the abdominal pain when food entered the gastrointestinal tract, and for the motor delay is not clear although it has its analogies with intermittent claudication and with angina.

Although frequent reference is made in general articles (e.g., in the excellent one of Klein) to the occurrence of chronic abdominal pain in vascular disease, specific examples with data relative to findings at postmortem are rare, nor do they supply sufficient material for the description of clear-cut clinical entities except in the broadest suggestive outlines. The accompanying tabular summary includes only those cases in the literature in which the findings at necropsy are stated.

* In the event of complete occlusion of the superior mesenteric artery, however, sufficiency of the collateral circulation is rare. There are, nevertheless, several striking exceptions. Nazari renders an account of six patients in whom old thrombi were seen to occlude the trunk of the superior mesenteric artery although the intestines were not infarcted. In one of these the inferior mesenteric artery was twice its usual size. A very remarkable example of a normal intestinal tract in the presence of obliteration of both the celiac and mesenteric trunks was described by Chiene in a dissecting room subject (1868). The blood supply was derived by anastomosis of the gastrointestinal vessels with greatly enlarged lumbar arteries.

Chronic Cases of Abdominal Pain Associated with Vascular Disease

Sex and Age	Chief Symptoms	Duration	Laboratory and Physical Findings	Course	Pathology	Source and Date
Female 48	Repeated attacks of severe pain in the right hypochondrium. Profuse diarrhea, "coffee ground" stools. Numbness of left leg.	8 mos. "of late."	Abdominal tenderness and distention. Visible peristalsis. Gangrene of left foot.	Death soon after amputation of left leg.	Laminated clot about the mouth of the superior mesenteric artery. Entero-colic and entero-enteric fistulas. Thrombosis of left common iliac artery and vein.	Howse 1878
Male 40	Intense abdominal neuralgia.	5 yr.		Found unconscious.	Calcified mesenteric lymph nodes compressing the trunk of the superior mesenteric artery. Thrombosis of superior mesenteric artery. Hemorrhagic infarct of intestine.	Lépine quoted by Adenot 1890
Female 55	Constipation relieved only by enemata. Pain in epigastrium, rt. hypochondrium and umbilicus; recently of special intensity and coming after meals. Almost continuous pain in the lower abdomen.	5 yr. 4 yr. To 6 mo. before admission. Past 6 mo.	Vital signs normal. Abdomen, soft, sensitive in the epigastrium.	Operation: gallbladder showing slight chronic cholecystitis removed. No relief of symptoms. Death suddenly 1½ mo. after operation.	Complete obliteration of superior mesenteric artery by an old organized thrombus. Fibrino-hemorrhagic peritonitis. Infarct of small intestine.	Schnitzler 1901

Chronic Cases of Abdominal Pain Associated with Vascular Disease—*Continued*

Sex and Age	Chief Symptoms	Duration	Laboratory and Physical Findings	Course	Pathology	Source and Date
Male 55	Pain in region of umbilicus and in right lower quadrant, severe distention 1½ hr. after each heavy meal. Constipation relieved by enemata.	2 years. Several remissions. Present attack: 3 mo.	Marked distention of abdomen 2 to 3 hrs. after eating.	Death 1½ days after exploratory laparotomy.	Extensive arteriosclerosis of superior and inferior mesenteric arteries including their finer branches; distention of entire gastrointestinal tract. Peritonitis.	Ortner 1902
Male 41	Abdominal pain, nausea and feeling of rapid fullness after eating. Admitted in emergency on account of attack of extremely severe abdominal pains, blood in vomitus and stools.	21 months.	Wassermann reaction positive. Normal gastric analysis. Pallor, sweating. Slight diffuse distention. Slight muscular guarding. W.B.C. 18,000. Temp. 38.2°C.	Operation performed under diagnosis of perforated gastric ulcer. Infarct found. Resection of 1 meter of upper ileum. Patient died soon after.	Thrombi, sessile upon ulcers of aorta, one of which acted as a flap valve over the mouth of the superior mesenteric artery.	Störring 1934

Clinically pain was the most prominent symptom. The duration varied from eight months to five years. Most often it was in the periumbilical region or right side. In three instances it was stated to be associated with ingestion of food—appearing one to three hours later. Moynihan remarks that "the greater suffering caused by heavy meals as compared with the less suffering after light meals is most significant." Distention accompanied the pain to a striking degree in one patient, and a feeling of fullness and of nausea in another. Two suffered from diarrhea, but in two constipation relieved only by enemata was the characteristic symptom. Vomiting was rare. The most constant recorded features on physical examination were abdominal tenderness (four patients) and distention (three patients). The abdomen was soft to palpation.

The anatomical changes were diverse. In one case a laminated clot narrowed the mouth of the superior mesenteric artery, in another a thrombus sessile upon an atheromatous ulcer acted as an obstructing valve and in Schnitzler's patient an old thrombus completely occluded the trunk of the vessel. In one postmortem examination calcified mesenteric lymph nodes were seen to compress the superior mesenteric trunk. In Ortner's case there was extreme arteriosclerosis of the superior and inferior mesenteric arteries including their finer branches. It is of interest that infarction of the small intestine with peritonitis was the terminal event in three of five recorded cases and also in the subject of the present report. Operation was followed by death in all of the four patients on whom it was performed.

More difficult to interpret are the published clinical impressions without necropsy material (Gilbride, Meyer, Goodman, Hamburger). Their chief value is in the light that they shed on possible treatment. The clinical descriptions are in agreement with those summarized in the table. Gilbride emphasizes the tenderness of the abdominal aorta, the epigastric or umbilical pain that may increase during digestion, upon exertion, in association with emotional disturbances or upon assumption of the horizontal position. Remarkable is the relief reported to be obtainable with various vasodilators. Hamburger has used nitroglycerine in doses of gr. 1/50 with success as has Gilbride. Buch and the latter recommend strophanthus and theobromine sodium salicylate.

Among the diseases to be considered in the differential diagnosis are the colics, renal, biliary, intestinal and that associated with plumbism, peptic ulcers, abdominal aneurysms, gastric crises of tabes, and above all carcinoma where the possibility of relief by surgery exists. True anginal heart disease with pain referred to the abdomen is usually accompanied by substernal pain (Buch). The use of vasodilators may serve as a therapeutic test, but all available physical and laboratory methods should be employed to rule out non-vascular disease.

Conclusions

The symptoms associated with abdominal arteriosclerosis, as shown by the five cases reported in the past and the present case, are usually of upper abdominal pain sometimes associated with the ingestion of food, abdominal tenderness and, to a lesser degree, distention and feeling of fullness. Either constipation or diarrhea may be present. Vascular disease should be more often considered in the differential diagnosis of chronic abdominal pain than heretofore. This is all the more important because of the great danger of operation in such

cases and the possibility of securing relief by the use of vasodilators. It is obvious that further study with careful clinical, roentgenographic, electrocardiographic and necropsy reports are necessary.

Note: Since this paper has gone to press, another article on this subject has appeared: DUNPHY, J. E.: Abdominal pain of vascular origin, Am. Jr. Med. Sci., 1936, cxcii, 109–113.

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PRIMARY PNEUMOCOCCIC PERITONITIS; RECOVERY OF THE ACUTE SEROUS TYPE FOLLOWING TYPE I SERUM TREATMENT WITHOUT SURGICAL INTERVENTION *

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PNEUMOCOCCIC peritonitis is comparatively uncommon and bears a grave prognosis. It is generally divided into two types, primary and secondary. The primary type is characterized by involvement of the peritoneum without any discernible focus of infection and it tends to run one of two courses. The most common course is an acute diffuse serous peritonitis that usually ends quickly in exitus. The second course results in a localized and circumscribed abscess of the peritoneum and is associated with a more favorable prognosis. In the secondary type of pneumococcic peritonitis we find an antecedent or coincidental source of infection, usually the respiratory tract, with subsequent development of peritonitis.

In primary pneumococcic peritonitis, the majority of cases have been treated surgically with a very high mortality, especially in the acute diffuse type. Lipshutz and Lowenburg [1] had a mortality of 100 per cent in a group of 13 cases reported in 1926.

In our review of the literature, recovery in a patient with the acute serous type of primary pneumococcic peritonitis, without surgical intervention, and with specific serotherapy has previously not been reported. The purpose of this paper is to report such a case with dramatic recovery following the therapeutic use of specific serum.

CASE REPORT

M. M., female, aged five, entered the Beth Israel Hospital on January 6, 1935, complaining of abdominal pain and fever.

Past History: This included whooping cough at the age of 10 months, measles at the age of two years, pneumonia one year previously. The patient was known to be sensitive to various foods and had received diphtheria toxin and antitoxin immunization. There was a family history of bronchial asthma. According to the parents, the child developed an upper respiratory infection 10 days before admission, characterized by a slight non-productive cough, unassociated with temperature or malaise. Seven days before admission, the child complained of twinges of abdominal pain, not severe in nature, nor incapacitating. This episode was repeated five days before admission. Throughout this period she was up and about, attending school. During the evening prior to admission, the child complained of a "bellyache." On the morning of admission, she ate a good breakfast, and had no complaints, but in the afternoon she developed anorexia and lassitude and a temperature of 104.5° F. by rectum. During the inspection of the throat the patient vomited for the first time. The vomiting was non-projectile in nature. In the afternoon the patient suddenly developed severe generalized abdominal pain and was found to be writhing in agony. These cramps continued intermittently until 6 p.m. The child became extremely toxic and was referred to the hospital.

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Physical examination revealed a well developed, well nourished child with flushed face lying in bed, talkative and coöperative. Temperature 105° F., respirations 30, pulse 150. The throat showed only mild injection without exudate. The examination was otherwise negative except for a distended abdomen showing moderate involuntary spasticity most severe in the right lower quadrant. By rectal examination, there was more tenderness in the right lower quadrant than the left.

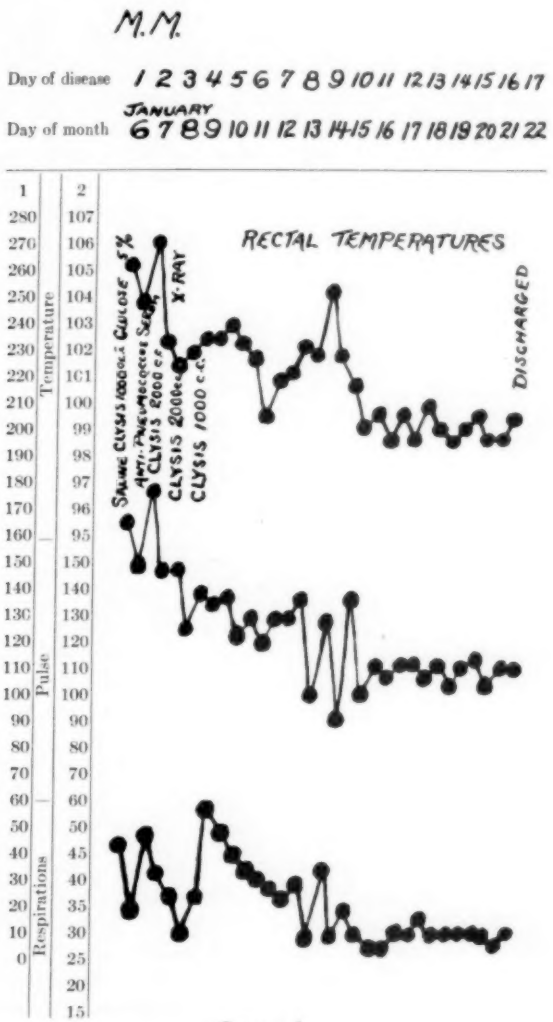
M.M.
Day of disease 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Day of month JANUARY 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
RECTAL TEMPERATURES
DISCHARGED
X-RAY
Temperature
Pulse
Respirations

CHART 1.

Clinical Course: Upon admission (evening of January 6, 1935) patient was put in high Fowler's position. All fluids by mouth were restricted and the water balance maintained by an intravenous drip of 2.5 per cent glucose in normal saline solution. Distension was controlled by flaxseed poultices and rectal tube. Morphine sulphate gr. 1/24 was given subcutaneously every three hours. Admission blood culture (read after 14 hours' incubation) showed many colonies of gram positive diplococci. On typing, this was found to be Type I pneumococcus. The admission urine showed a

specific gravity of 1.036, v.s.t. of albumin, 2.5 per cent sugar, 3 plus acetone, one to three pus cells per high power field. The admission white count was 14,400 per c.c. The admission red count was 4,100,000 per c.c., hemoglobin 80 per cent. Throat smear on admission showed many gram positive diplococci and streptococci. Roentgen-rays of the chest were negative.

The next day (January 7, 1935), the temperature rose to 106.5° by rectum, pulse 172, respirations to 44. The patient was markedly dehydrated, wildly delirious, toxic and completely irrational. The patient was controlled by the constant care of extra nurses daily (two on a shift). Paraldehyde was given by rectum for restlessness. The white blood count rose to 18,400. Stool examination showed no blood on Guaiac test. The abdomen was definitely more spastic throughout with increased resistance in both lower quadrants where the patient also, in her more lucid moments, noted more pain on pressure. The heart and lungs were negative. During the evening the patient was started on antipneumococcus serum therapy as described in the chart. The intravenous drip of 2.5 per cent glucose in salt solution was continued and two clyses of 1000 c.c. of saline and glucose were also given.

On January 8, 1935 (the second hospital day), the day after the administration of serum, the abdomen was somewhat softer. The patient was rational, no pain was noted on pressure about the umbilicus. There was some tenderness in both flanks, however, and both lower quadrants. The temperature, pulse and respiration dropped to 102° (by rectum), 140 and 25, respectively. The intravenous use of serum was continued as described in the chart.

On January 9, 1935 (the third hospital day), the patient continued rational and became brighter, more cheerful and talkative. Intravenous drip was discontinued and the patient was allowed cracked ice and sips of water as desired. The intravenous use of serum was continued. The temperature remained about 102° rectally and the pulse went down to 130. The second blood culture was negative (no growth on culture media after nine days). The white count dropped to 9,100 per c.c. in the morning and to 7,700 in the evening. The patient's fresh blood serum agglutinated Type I and Type II pneumococcus microscopically. Type I pneumococcus was agglutinated in dilution of one to two only. On January 10, 1935 (the fourth hospital day) the patient developed a cough and hiccup on respiration. Roentgen-ray of the chest was negative. There was tenderness at the right and left upper quadrants. Respiration 48. (See clinical chart.) During the next four days the spasm and tenderness in the abdomen diminished so that there was some residual tenderness only in both lower quadrants. The abdomen became "doughy" to touch, abdominal distention was present and a fluid wave could be felt. Distention was controlled by flaxseed to the abdomen and by a rectal tube. The temperature remained 102° F. rectally. The patient continued bright, talkative and cheerful. Fluids by mouth, up to three ounces at a time, were well tolerated. The final dose of serum (8 c.c.) was given intravenously. A third blood culture taken on this day proved to be negative. The patient's fresh blood serum showed complement in low titer as measured by activation of sheep cell hemolysis. Fresh blood serum agglutinated Type I and Type II pneumococcus microscopically and macroscopically. The serum agglutinated Type I pneumococcus in dilution of 1–4, but failed to agglutinate Type II pneumococcus. One liter of urine was concentrated to 5 c.c. From this an attempt was made to recover specific substances, but the alcohol insoluble material contained no substances which would precipitate Type I antipneumococcus serum.* The white count was normal. The urine showed no sugar, albumin or acetone; sediment negative.

On January 11, 1935 (the fifth hospital day) the patient continued to improve, the temperature remained about 100° F. rectally, and most of the abdominal signs and symptoms disappeared. The white count was normal and the urine was negative.

* We are indebted for the performance of these tests to Dr. Maxwell Finland, who also assisted in directing the sero-therapy.

On January 12, 1935 (the sixth hospital day) the patient's temperature dropped to 98.6° F. rectally in the morning. In the afternoon, the patient developed serum sickness, characterized by fever (104.4° F. by mouth), arthralgia and rash. This subsided in four days. Further convalescence was uneventful with blood and urine normal and the patient was discharged on January 22, 1935, the sixteenth hospital day.

Comment

There have been many differing views regarding the mode of infection in primary pneumococcus peritonitis. The peritoneum may presumably become infected (a) through the gastrointestinal tract; (b) by way of the blood stream; (c) from the vagina through the fallopian tubes to the pelvic peritoneum. The evidence in favor of the transdiaphragmatic lymphatic route is meager. The direction of the lymphatic drainage in the region of the diaphragm has been shown to be upwards. There have been some proponents of the theory that pneumococci reach the peritoneum by egress from the intestinal tract. However, Jensen,[2] Wolfsohn,[3] and McCartney and Fraser,[4] were unable to produce peritonitis by feeding cultures of pneumococci to mice, even though the former demonstrated pneumococci in the intestinal wall. Obadalek [5] and Koennecke [6] concur in the belief that pneumococci in feces may produce peritonitis by contamination of the genital tract in females. Rischbieth [7] and others advance the view that pneumococcic peritonitis is always secondary to a septicemia. Pneumococcic septicemia, however, is a very frequent concomitant of lobar pneumonia, which is very rarely complicated by peritonitis. Rolleston [8] found 11 cases of peritonitis in 4454 cases of pneumonia, Rischbieth only one case in 6000 pneumonias and Elkin [9] three in 1908 cases. Blake and Cecil [10] were unable to produce pneumonia or peritonitis by intravenous injection of pneumococci, the animals dying of septicemia. On the other hand, Jensen [2] showed that pneumococci reached the blood stream in a rabbit a few minutes after intraperitoneal injection. These experiments were confirmed by McCartney and Fraser. Apparently other factors in addition to the mere presence of pneumococci in the blood stream are necessary to produce peritonitis. Peiser [11] suggested that the uninjured peritoneum was impermeable to the invasion of organisms from the blood stream. This may account for the increased frequency of peritonitis in association with nephrosis with ascites. McCartney and Fraser [4] made a detailed study of the mode of infection and found no evidence in favor of either the hematogenous or enterogenous theories. They regard all cases of primary or idiopathic pneumococcic peritonitis as arising from the genital tract and of necessity therefore, limited to the female sex. In their study of 56 cases, they claim that the 12 cases occurring in boys were all of the secondary type. Barrington-Ward [12] and others, however, have reported cases in boys. In one case reported by Leonardo, the disease developed in a woman who had had an amputation of the uterus 15 years previously. Nevertheless, the overwhelming incidence in girls points strongly toward the genital tract as the chief source of infection with an occasional case arising via some other route.

Diagnosis. The primary type occurs most frequently in children between the ages of two and seven. The disease is usually characterized by an abrupt onset of severe abdominal pain, chiefly localized in the lower abdomen. Vomiting and diarrhea may occur, the latter sometimes associated with tenesmus. Hyperpyrexia, prostration, delirium and dehydration are other features. Cases

with a more chronic course have been reported with and without an associated intraabdominal localization of the purulent process. As a rule the more chronic type of case has a much better prognosis. A milder form with a spontaneous recovery has also been observed and described as an abortive type.[13] In suspected cases immediate blood culture is of paramount importance since many of these cases are associated with a pneumococcic septicemia. We have already mentioned that experimentally the blood stream shows the presence of organisms within a few minutes after intraperitoneal injection. Frequent smears from the culture medium should be made. As soon as organisms are discovered typing should be at once performed.

In the differential diagnosis one must consider chiefly acute appendicitis with or without perforation and subsequent peritonitis, and peritonitis due to the streptococcus. In most cases the diagnosis of appendicitis was made when the patients were first seen, and not until after an examination of the abdominal fluid at operation was the correct diagnosis made. In suspected cases abdominal fluid may be obtained by abdominal paracentesis. In 100 cases Neuhoff and Cohen[14] demonstrated that this was an innocuous procedure. Other authors advocate puncture of the pouch of Douglas in females.[15] In some cases pneumococci have been found in vaginal smears.

An attempt to type the pneumococcus should always be made immediately irrespective of the source of the organism. There are no reliable statistics to indicate the actual frequency of the various types of pneumococci found in primary pneumococcic peritonitis. Prior to 1926, Leonardo[16] found a total of 22 cases in the literature where the organisms were typed; 16 were Type I, 3 Type II and 3 Type IV. Since then the marked paucity of complete bacteriological studies has been striking, most of the authors being content with determining the generic organism.

The indefinite character of the patient's symptoms prior to admission precludes any estimation as to the time of onset of the peritonitis. This child had a history of a mild upper respiratory infection about a week preceding the onset of the peritonitis and examination of the throat failed to reveal any definite abnormality. The negative physical examination of the chest and the repeated roentgen-rays ruled out the lungs as the source of the infection. However, the patient's course was fulminating with hyperpyrexia during the day of entry.

The diagnosis was based upon (1) history of an upper respiratory infection (present in 90 per cent of the cases reported by Lipshutz and Lowenburg[1]). (2) Onset of severe abdominal pain with signs of an acute "surgical" abdomen. (3) Temperature that varied between 105 and 106.6° F. rectally. (4) Rapid prostration and delirium. (5) Positive blood culture (Type I pneumococcus).

It was the unanimous opinion of all who saw the patient that surgical intervention was not indicated*; it was felt that her condition was so critical that an operation would be fatal.

In view of the presence of Type I pneumococci in the 14 hour blood culture immediate sero-therapy was instituted with the results indicated in the clinical course and in the chart.

Cases have been reported where a Type I pneumococcus was found at operation and sero-therapy was instituted after operation.[17] We have been un-

* Dr. C. G. Mixter and Dr. D. D. Berlin as surgical consultants and Dr. E. H. Place as consulting pediatrician were all opposed to surgical intervention.

able, however, to find a case of primary fulminating pneumococcic peritonitis (i.e., acute serous type) treated solely by specific serum. In 1924, Struther [18] stated that he "was able to find no information on the use of specific sera in pneumococcic peritonitis." Although Barrington-Ward suggested the use of specific serum in the outline of treatment, none of his cases had received serum. Fricke [19] reported one case, an adult, of the more favorable chronic type, who was given serum and recovered without operation. He does not state how long the condition existed before giving the serum. The clinical condition of our patient was so critical and her response to serotherapy was so pronounced that it is unlikely that a spontaneous remission in the disease had taken place.

Serum Chart

1/7/35	9:30 p.m.	0.04 c.c.	of Massachusetts anti-pneum. serum in left forearm intracutaneous.
	9:36 p.m.		Wheal 6 mm. not sharply demarcated and without pseudopods and 2.2 cm. of faint erythema.
	10:00 p.m.		No change. Control negative.
	10:00 p.m.	0.08 c.c.	Serum subcut. in left infradeltoid region.
	10:20 p.m.		No local reaction. Skin test has faded completely.
	10:30 p.m.	0.30 c.c.	Subcut. over deltoid. No reaction.
	11:00 p.m.	0.80 c.c.	Subcut. over deltoid. No reaction.
	11:30 p.m.	0.20 c.c.	Intramusc. in deltoid. No reaction.
	11:55 p.m.	15 c.c.	Father's serum intragluteally. No reaction.
	12:00 p.m.	0.8 c.c.	Intramusc. into deltoid.
1/8/35	12:30 a.m.	0.5 c.c.	Intravenously; over at 12:38.
	12:50 a.m.		Rash over left chest, face, body blotchy, no wheals.
	12:50 a.m.		Respirations irreg., face slightly cyanotic. Inspir. and expir. wheezes in right chest, prolonged expirations—P. 150.
	12:55 a.m.		Adrenalin 1/1000 0.3 c.c. intradeltoid.
	1:00 a.m.		Resp. regular, wheezes disappeared, rash almost completely faded. T. 1:30 a.m. 106.4.
	2:30 a.m.		Blotchy rash re-appears on chest and abdomen. No resp. distress.
	3:10 a.m.		Rash more punctate on chest.
	3:30 a.m.	5.0 c.c.	Intrav. Injection over at 3:36. Splotchy rash over chest, abdomen, shoulders at 3:39. Resp. 42, reg. No wheezes.
	3:45 a.m.		P. 144. Occas. rhonchus right chest.
	3:53 a.m.		Rhonchi both lung fields. Audible resp.
	3:55 a.m.		Adrenalin 1/1000 0.3 c.c.
	3:56 a.m.		Blanching of diffuse rash on chest.
	3:57 a.m.		Rhonchi disappeared.
	4:00 a.m.		Rash gone on face.
	4:15 a.m.		Rash on body gone.
	4:22 a.m.		Adrenalin 1/1000 0.2 c.c. Rhonchi with respirations.
	4:47 a.m.		No rhonchi. Lips somewhat cyanotic.
	7:43 a.m.	7.0 c.c.	Intrav. Injection over at 8:50.
	7:56 a.m.		Mottled rash on left arm.
	7:58 a m.		Wheal over left deltoid, diffuse rash over upper thighs.
	8:14 a.m.		Wheal and rash of left deltoid is blanched.
1/8/35	10:55 a.m.	15 c.c.	Dr. Finland's blood serum intragluteally.
	11:00 a.m.	8.0 c.c.	Serum intravenous, injection ended 11:07. Blood culture previously taken. 11:00 a.m. T. 102°. P. 140. R. 25. Rough systolic murmur. Abdomen more flaccid in epigastrium. Still tense in lower abdomen and somewhat distended. No rash or rhonchi.
1/8/35	3:10 p.m.	8.0 c.c.	Intrav. T. 101.8°, P. 140, R. 32. Injec. over at 3:17.
	7:15 p.m.	8.0 c.c.	Serum intrav.
	7:17 p.m.		Generalized reddish blush, disappeared in 2 min.

Serum Chart—Continued

1/9/35	12:04 a.m.	6.0 c.c.	Serum intrav. Injec. completed at 12:09. Generalized blush lasting 1 min. and fading. No rhonchi.
	10:30 a.m.	8.0 c.c.	Serum intrav. injected in 4 min. Generalized blush immediately.
	10:35 a.m.		Faded.
	10:36 a.m.		Blotchy rash on hands (palms) present.
1/10/35	12:15 p.m.	8.0 c.c.	Serum intrav. Injected in 5 minutes.
	12:21 p.m.		Slight flush to face.
	12:22 p.m.		Coughing, no wheezes. Wheal 4 cm. at site of injection. Erythema 1 cm. about wheal.
	12:35 p.m.		Wheal disappeared.
	12:48 p.m.		Erythema disappeared.
1/12/35			Papular red rash around pubis, buttocks and ankles.
1/13/35			Macular blotchy rash, itchy, over cheeks, wheals over left upper arm. Still coughing. Eyelids edematous. Disappeared in p.m.
1/13/35	11:30 a.m.		Blotchy raised rash on face and outer thighs. Wheals and marked itching.
Condition:			Improved.
Diagnosis:			Idiopathic pneumococcus Type I peritonitis.

The usual leukocytic response in pneumococcic peritonitis resembles more that of an acute septic type of hyperleukocytosis than the moderate elevation found in the ordinary cases of acute appendicitis. Glass [20] commented on the frequency with which counts of 30,000 or more are encountered in pneumococcic peritonitis. Gibson [21] stressed the extraordinarily high leukocyte count with a high percentage of polymorphonuclears as a valuable point in differentiating this type from the appendiceal and non-pneumococcic forms of peritonitis. The white blood cell counts in this case did not conform to Gibson's formula; the highest being 18,400. However, Lazarus [22] has noted similar low counts in several patients critically ill with the acute serous type of primary pneumococcic peritonitis.

Summary

Primary pneumococcic peritonitis is a disease occurring chiefly in female children. The mortality rate is very high, both in operated and unoperated cases, especially in the acute serous type of primary pneumococcic peritonitis. A case of this severe type of primary pneumococcic peritonitis with Type I pneumococcic septicemia which responded to the administration of specific serum, is reported. Complete recovery without complications ensued and the patient was discharged in 16 days. In view of the fact that pneumococci reach the blood stream early in the course of this infection, repeated blood cultures are indicated in every patient in the hope of finding a type amenable to specific sero-therapy.

Conclusions

Early specific sero-therapy in the treatment of primary pneumococcus peritonitis, we believe, offers a non-surgical method of attack, which may prove valuable in selected cases and should be given wider trial.

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THROMBOPENIC PURPURA ASSOCIATED WITH CATARRHAL JAUNDICE: REPORT OF A CASE*

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A patient has been observed in whom an acute thrombopenic purpura occurred simultaneously with an acute catarrhal jaundice. The case is reported because of its uniqueness † and because of some of the theoretical implications involved.

Case Report

A. O., a single, male medical student, aged 24, entered the Passavant Memorial Hospital on November 3, 1934, complaining of malaise, epistaxis and jaundice.

* Received for publication August 17, 1936.
From the Department of Medicine, Northwestern University Medical School.
† No similar case report could be found in the literature.

Laboratory Data During Remission of Thrombopenic Purpura and Jaundice

Date Nov. 1934	RBC mill. per cu. mm.	Hgb. gm. per 100 c.c.	WBC per cu. mm.	Platelets per cu. mm.	Bleeding Time min.	Clot Retraction	Urine		Feces Blood Benzidine Test	Van den Bergh mg. per 100 c.c.	Icterus Index Units	Liver Function
							Blood	Bile				
11-3	5.00	16.0	9950	none	20+	none	50 cells h.p.f.*	+++				
11-5	5.36	16.0	5500	none	15	none	gross	+++	++++	7.0	90	
11-7				30,000	5		gross		++++			
11-8	5.17	15.6	5500	60,000	3	fair	75 cells h.p.f.	+++	+++	6.7	70	Bromsulphalein (2 mg. per kilo) 5 min. 90% dye retention, 30 min. 50% dye retention
11-9							10 cells h.p.f.	++	+++		60	Levulose (50 grams) Hrs. 0 ½ 1 2 3 Mg.† 77 107 116 104 87
11-12				230,000	2		0	+	0		25	
11-19	4.34	13.4	7000	370,000	2		0	0	0	0.7	20	Bromsulphalein (2 mg. per kilo) 5 min. 40% dye retention, 30 min. 10% dye retention

* h.p.f. high power field.
† mg. reducing substance per 100 cc. blood.

History: The family history and past history were irrelevant. The present illness began October 1, 1934, when the patient contracted an upper respiratory infection. Following this, he felt below par. On October 30, he had loss of appetite, muscular aching, constipation, and discomfort in the abdomen. The next day the urine was highly pigmented, and the stools lighter than normal. The following day (November 1), the patient noticed slight icterus and remained in bed. On November 2, he had nose bleeds, and petechial spots appeared on the trunk. He continued to have light stools and constipation, but the aching and abdominal discomfort subsided. The patient was admitted to the hospital the next evening. No drugs had been taken during this illness.

Physical Examination: The physical examination revealed a well nourished, somewhat apprehensive young male who did not appear to be very ill. There was bleeding from the left nostril. The sclerae and skin were moderately icteric. Numerous petechial hemorrhages were present on the lips and gums, and were also scattered all over the body. Subcutaneous hemorrhage was not readily produced by pinching the skin. The heart and lungs were normal. The liver was not palpable, but the tip of the spleen was palpated at the costal margin on deep inspiration. The temperature was 98.8° F., pulse 80, and respiration 20. The blood pressure was 114 mm. of Hg systolic, 70 mm. diastolic.

Laboratory Examination: The significant laboratory data are best presented in tabular form (see table). It is apparent that the laboratory signs were those of thrombopenic purpura with bleeding from the kidneys and the gastrointestinal tract. The direct Van den Bergh test showed a positive prompt and negative delayed reaction, while the indirect quantitative test and icterus index were markedly increased. The bromsulphalein test showed a marked retention of the dye when performed on the fifth day, while the levulose tolerance was practically normal when first studied on the sixth day after admission.

Additional laboratory data not listed in the table revealed the following: Reticulocyte counts on two occasions, less than 1 per cent. Erythrocyte volume index, 1.06. Fragility test, within normal limits. Differential: polymorphonuclear neutrophiles; band forms 0, segmented forms 67 per cent; lymphocytes 21 per cent; monocytes 12 per cent. Coagulation time, 2 minutes. Urine pigmented, contained erythrocytes. Feces dark brown; $HgCl_2$ test for urobilin and bilirubin negative; benzidine test markedly positive. Blood calcium, 10.9 mg. per 100 c.c.

On the fourth day after admission, a tube was inserted into the duodenum, and a thin greenish mucoid secretion was obtained after administration of 100 c.c. of magnesium sulphate. Inoculation of the patient's blood into a guinea pig showed a negative test for Weil's disease.

Course and Treatment: No fever or tachycardia occurred at any time during the course of the disease. On the second day after admission (November 5), the patient received a transfusion of 250 c.c. of citrated blood, and the following day 50 c.c. of whole blood into the buttocks. Beginning November 5, parenteral liver extract (1 c.c. derived from 33 1/3 gm. liver *) and calcium gluconate and viosterol were given daily. For three days after admission, the petechiae increased, bleeding from the nose became more severe, and there was an increase in bleeding from the kidney and gastrointestinal tract. On November 6, the patient began to improve, and by November 8 all gross bleeding had stopped. Clinical and laboratory signs of the thrombopenic purpura rapidly returned to normal. At the same time, there was continuous improvement in the jaundice. The patient was discharged from the hospital November 24, three weeks after admission, in excellent condition. There has been no recurrence of symptoms up to the present time, one and one-half years after the illness occurred.

* Lederle's Concentrated Liver Extract.

Comment

The thrombopenic purpura and jaundice in this patient began at about the same time and ran a similar course. The improvement that occurred following the blood transfusion and liver therapy may have been a coincidence. From the clinical picture, the jaundice was apparently of the catarrhal type. Whether actual liver damage occurred or not is uncertain. Many authors [1, 2, 3, 4, 5] have reported a decreased galactose tolerance in patients with catarrhal jaundice and have usually interpreted this as being evidence of parenchymatous liver disease. In our case, the levulose tolerance curve was practically normal when first studied on the ninth day of the illness. This does not preclude an earlier pathologic curve, as Jolliffe [6] has shown that the decreased levulose tolerance in catarrhal jaundice may return rapidly to normal shortly after the blood bilirubin reaches its peak.

There are several theories that might explain the etiologic relationship between the thrombopenic purpura and the catarrhal jaundice, namely, (1) they may have occurred independently, (2) they may have been caused by the same etiologic process, and (3) the purpura may have been secondary to the catarrhal jaundice. The latter theory will be considered further, because certain reports in the literature suggest that thrombopenia may be related to liver disease.

The bleeding tendency that often accompanies jaundice and liver disease is not usually of the thrombopenic type. However, exceptions to this rule have been reported. Loeper and DéSeze [7] observed a patient in whom purpura occurred along with metastatic carcinoma of the liver. The patient had numerous petechiae, a prolonged bleeding time, a normal coagulation time, and a delayed clot retraction. The platelet count was not reported. Willebrand [8] described three cases in which thrombopenic purpura was associated with liver disease. Two of his patients had metastatic carcinoma of the liver, and a third had an acute yellow atrophy of the liver following salvarsan therapy. Recently, Abrami [9] discussed this subject under the title of hepatic purpura. He described two cases, one of atrophic cirrhosis and another of spleno-hepatic disease of syphilitic origin. Both patients had purpura, a prolonged bleeding time, a positive tourniquet test, and non-retraction of the clotted blood. The platelet count was not reported in the first case, but was 82,000 per cu. mm. in the second. Splenectomy was specific in controlling the hemorrhagic tendency in both cases. Abrami believes that true purpura in liver disease is due to involvement of the "spleno-reticulo-endothelial" system and is not due to the liver insufficiency per se.

Very few data on the platelet count in liver disease are available in standard reference books. Jones and Minot [10] estimated the number of platelets on blood films from patients with catarrhal jaundice and found them to be within normal limits. During recovery from the disease, there was an increase in the thrombocytes. Weil et al. [11] reported a diminution in platelets in 18 out of 20 patients with liver lesions. Their series consisted mainly of cases of cirrhosis and chronic congestion of the liver. King [12] found a thrombopenia in 20 per cent of patients with portal cirrhosis of the liver. Fellinger and Klima, [13] studying a group of patients with cirrhosis of the liver, frequently found a decrease in platelets which was related to the degree of liver involvement. In one advanced case, the platelet count was 20,000 per cu. mm., the bleeding time was

prolonged, and the clotting time was normal. The thrombocyte level is said to be low in acute yellow atrophy of the liver.[14, 15] Higgins and Stasney [16] reported a decrease in platelets to one-third of normal in rats with cirrhosis of the liver produced with carbon tetrachloride. A diminution in the leukocytes or erythrocytes may also be associated with hepatic disease. Leukopenia is reported to occur in catarrhal jaundice [17] and cirrhosis of the liver,[12, 18] while anemia is frequently associated with various types of liver disease.[19]

The cause of the decrease in thrombocytes in liver disease is not apparent. As Abrami [9] has suggested, the decrease might well be related to an associated pathologic process in the spleen rather than to the liver condition itself. The influence of the spleen on the blood platelets is evident in such diseases as thrombopenic purpura and splenic anemia where splenectomy is followed by thrombocytosis. Another possible mechanism in the pathogenesis of the thrombopenia in liver disease might be through the deficiency of a nutritional factor necessary for thrombopoiesis. For example, the macrocytic anemia of advanced cirrhosis is thought to result from the inability of the liver to store a necessary hemopoietic principle.[19]

From the evidence presented, it seems possible that the thrombopenic purpura in the patient reported could have been secondary to the catarrhal jaundice. A case of this type is a stimulus to further clinical and experimental observations.

Summary

1. A case is reported in which thrombopenic purpura occurred simultaneously with catarrhal jaundice.

2. Evidence is presented which suggests a relationship between thrombopenia and liver disease.

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CHLOROMA; REPORT OF A CASE*

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CHLOROMA is not a common form of malignant tumor. Washburn [1] in a review of the literature through June 1929 found 162 cases. Since that time 32 more have been reported, bringing the total to 194.

Dock and Warthin [2] in 1904 published an exhaustive study of the clinical and histological features of the disease. Their conclusion was that, "chloroma is a tumor-like hyperplasia of the parent cells of the leukocytes, primarily in red marrow, the periosteum being secondarily involved."

In the past, opinions have been divided concerning the lymphatic or myelogenous origin of the neoplasm, but the general opinion at present would indicate that the majority of chloromas are myelogenous in origin.

The prognosis of patients with chloroma has been universally bad with two exceptions. The first, reported by Lecène,[3] was a case of a tumor of the humerus, which was treated by amputation and roentgen-ray therapy; the second, reported by Washburn,[1] was a case of tumor of the left frontal bone of the skull, with operative removal and subsequent roentgen-ray therapy. Swanson,[4] Rosenblum,[5] Doub and Hartman,[6] and others failed to find roentgen therapy to be of value in influencing the final outcome of the disease.

We believe the following case of chloroma cannot be classified as either lymphatic or myelogenous in origin as the tumor cell is a primitive blast which might conceivably differentiate into either a lymphocyte or a myelocyte.

CASE REPORT

Elizabeth S., white female, aged 13 years, was brought to the hospital February 21, 1936, because of weakness, anemia, and vomiting. She had been irrational for the preceding 24 hours.

* Received for publication August 7, 1936.

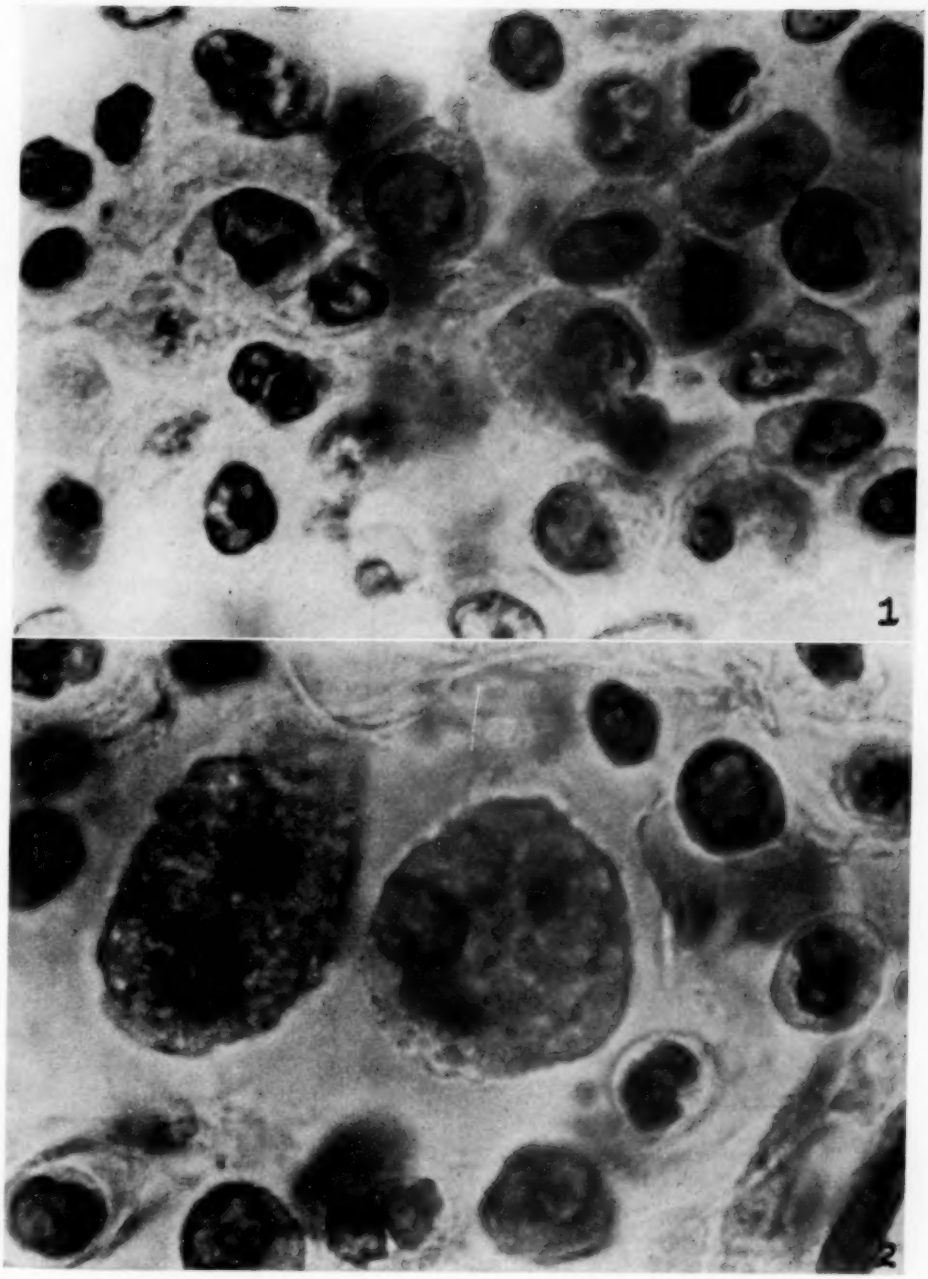

FIG. 1. No. 1. Chloroma. Neoplastic cells in a lymph node. (× 2070.)
No. 2. Endothelial phagocytes and tumor cells in the dura mater. (× 2070.)

In November 1935, the patient noticed swelling of the upper eyelids, severe enough at times to tightly close them. She rapidly became weak and pale. She complained of pain referred to the navel and vomiting. In December 1935, the vomiting grew worse, again accompanied by umbilical pain. In January 1936, her right eyelids suddenly became black and this was followed by the same phenomenon in the left eyelids a few days later.

January 10, she was taken to a hospital where she was diagnosed as suffering from malformations of both kidneys. She was given two blood transfusions with only transient benefit. Frequent nasal hemorrhages began. No bowel movements could be obtained. She was discharged January 25, slightly improved.

On February 12, 1936, persistent vomiting began and continued to the time of admission (February 21). There was a familial history of cancer.

Physical examination: The patient was extremely anemic and emaciated, irrational, and apparently almost deaf. She appeared to be nearly blind. The upper eyelids showed moderately firm swelling with dilated superficial veins. There was no exophthalmos. Crusts of dried blood were present in both external nares. The cervical, axillary, and inguinal glands were all palpable, discreet, and bean sized. There was an apical systolic cardiac murmur probably due to the anemia and not organic in origin. Examination of the chest revealed no evidence of disease. The abdomen was scaphoid with almost no panniculus. Tenderness was present in both upper quadrants but particularly the right. A smooth mass occupied the upper right quadrant from the ribs down to the level of the umbilicus. This mass was flat to percussion and poorly defined in outline, and appeared to be a greatly enlarged liver. The remainder of the examination was essentially negative.

Laboratory examinations: Ten consecutive urine analyses showed positive albumin, a trace of sugar, and fields full of granular casts and white and red blood cells. The specific gravity was fixed at 1.010. A blood count (February 21) showed hemoglobin 32 per cent (Dare), red blood cells 650,000 and white blood cells 10,100 per cu. mm., polymorphonuclear neutrophiles 47 per cent, lymphocytes 48 per cent, monocytes 5 per cent. Nothing abnormal was noted about any of the white blood cells. The sedimentation rate of the red blood cells was 44 mm. in 60 minutes (Cutler). Blood non-protein nitrogen was 28.5 mg. per 100 cubic centimeters. The stools contained four plus occult blood. The blood Kahn was negative.

Eye examination (February 27) revealed the following: The pupils reacted sluggishly to light and accommodation. They were dilated under homatropine and cocaine. No protrusion, nystagmus or paralysis of either eyeball was noted. The anterior and posterior chambers and lens were clear. Both eyes showed marked vitreous opacities. The fundus examination of the right eye showed over four diopters choking of the disc, with the vessels of the retina engorged and tortuous. There were marked masses of hemorrhage throughout the retina with small white areas noted in the center of the masses. The largest mass of hemorrhage was in the superior temporal portion of the fundus. A definite cherry-red spot showed around the fovea. The fundus examination of the left eye showed the same characteristics, except that the largest mass of hemorrhage was found posterior and towards the temporal side. A cherry-red spot also showed around the fovea and about two diopters choking of the disc was noted.

Roentgen-ray examination by Dr. J. E. Church (February 22, 1936) showed that the left lung field was a trifle more radiolucent than the right although no definite pathologic changes could be defined. An attempt was made to examine the upper gastrointestinal tract but the patient was non-coöperative and only a minute amount of barium was taken. A single anterior-posterior film was taken showing some of the meal had passed into the small intestine, which suggested that there was no obstruction of the pylorus. Some flakes of barium or bismuth which were found in

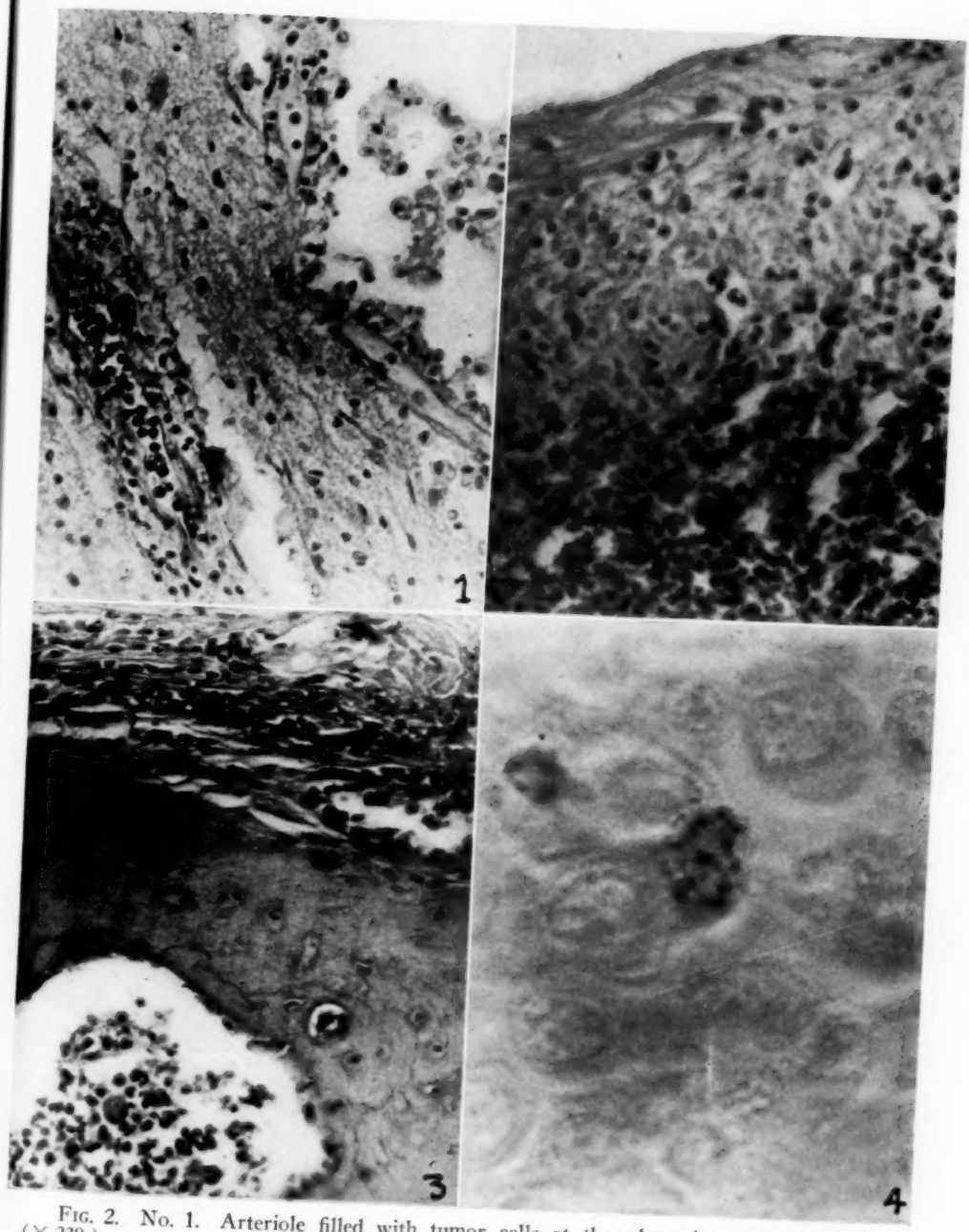

FIG. 2. No. 1. Arteriole filled with tumor cells at the edge of a cerebral vacuole. (× 230.)

No. 2. Tumor cell invasion of the dura mater. (× 230.)

No. 3. Pleural surface of a rib showing the tumor cell infiltration of the periosteum and marrow. (× 230.)

No. 4. Peroxidase granules present in a polynuclear leukocyte but absent in the tumor cells. (× 2070.)

the region of the rectum were due to some former examination or medication. The left kidney was not outlined, but the right was well defined, appearing as if it might be a little larger than normal.

A provisional diagnosis of lymphosarcoma with metastases to the brain was made as a result of the examinations.

Course of the disease: Twenty-four hours after admission the patient was given a transfusion of 500 cubic centimeters of whole blood with some transient improvement. The temperature ran an irregular course from 100° to 104° F. Five hundred cubic centimeters of 5 per cent glucose in normal saline were given twice daily. This was useful in controlling the persistent vomiting. Frequent hemorrhages from the nose occurred daily. The patient rapidly failed in spite of supportive treatment and expired March 1, 1936, nine days after admission.

Autopsy report: The autopsy was done one and one-half hours after death. External examination showed a female at the age of puberty who was markedly emaciated and very pale. There was moderately firm swelling of the upper eyelids.

Internal examination revealed about two liters of clear yellow fluid in the abdominal cavity. The liver and spleen were much enlarged. The mammary gland tissue was a bright olive green bilaterally. The costal cartilages cut with difficulty. The periosteum on the internal surface of the sternum and ribs was thickened and was almost uniformly bright green and the thymic fat in the anterior mediastinum was of the same color. About one liter of orange colored fluid was present in each pleural cavity and 100 cubic centimeters in the pericardial sac. There was one green spot on the anterior surface of the pericardial sac. The heart blood clots were maroon. No green areas were seen in the myocardium. The gross cardiac lesions were limited to a rather marked sclerosis of the aortic ring, involving the orifices of the coronary arteries. The lungs were bizarre in appearance having many reddish-purple and a few green slightly elevated areas over the surfaces of both lungs; the largest of these was not more than two centimeters in diameter. The peribronchial lymph nodes were uniformly olive green in color and varied in size up to one centimeter in diameter. The lungs were nodular on palpation, the nodules being the discolored areas described. On the cut surface there was revealed a bilateral bronchial pneumonia.

The liver measured 25 by 24 by 8.5 centimeters and was a maroon color. On the cut surface no gross tumor nodules were found and the liver lobules were distinctly outlined. The spleen measured 16.5 by 9 by 4.5 centimeters. The capsule was purple and tense. On the cut surface there were greenish spots scattered at intervals, none of them being over one-half centimeter in their greatest diameter. The peri-esophageal lymph nodes were green but the remainder of the gastrointestinal tract showed no green areas, and the mesenteric nodes though enlarged up to a maximum of 3 centimeters in size were maroon in color. The stomach showed petechial hemorrhages. The retroperitoneal lymph nodes were 2 centimeters in length and were olive green. The periaortic nodes had the same appearance.

The kidneys were studded with subcapsular green nodules up to 1 centimeter in diameter. The adrenals were small but showed no discolorations. The uterus showed several greenish nodules on the serosal surface, and the endometrium was olive green. The ovaries showed no gross pathologic change. The vertebral bodies had some greenish spots on their anterior surfaces and were unusually soft so that they could be cut easily with a knife. The ribs were almost as soft as the costal cartilages, and their bone marrow varied from maroon to olive green. The bone marrow of the sternum was maroon.

The periosteum of the skull was green near the midline, and was slightly thickened. The bones of the skull were harder than the ribs and vertebral bodies but still were softer than normal and their bone marrow was brown. The dura mater was thickened to one-half centimeter near the midline and was olive green. The

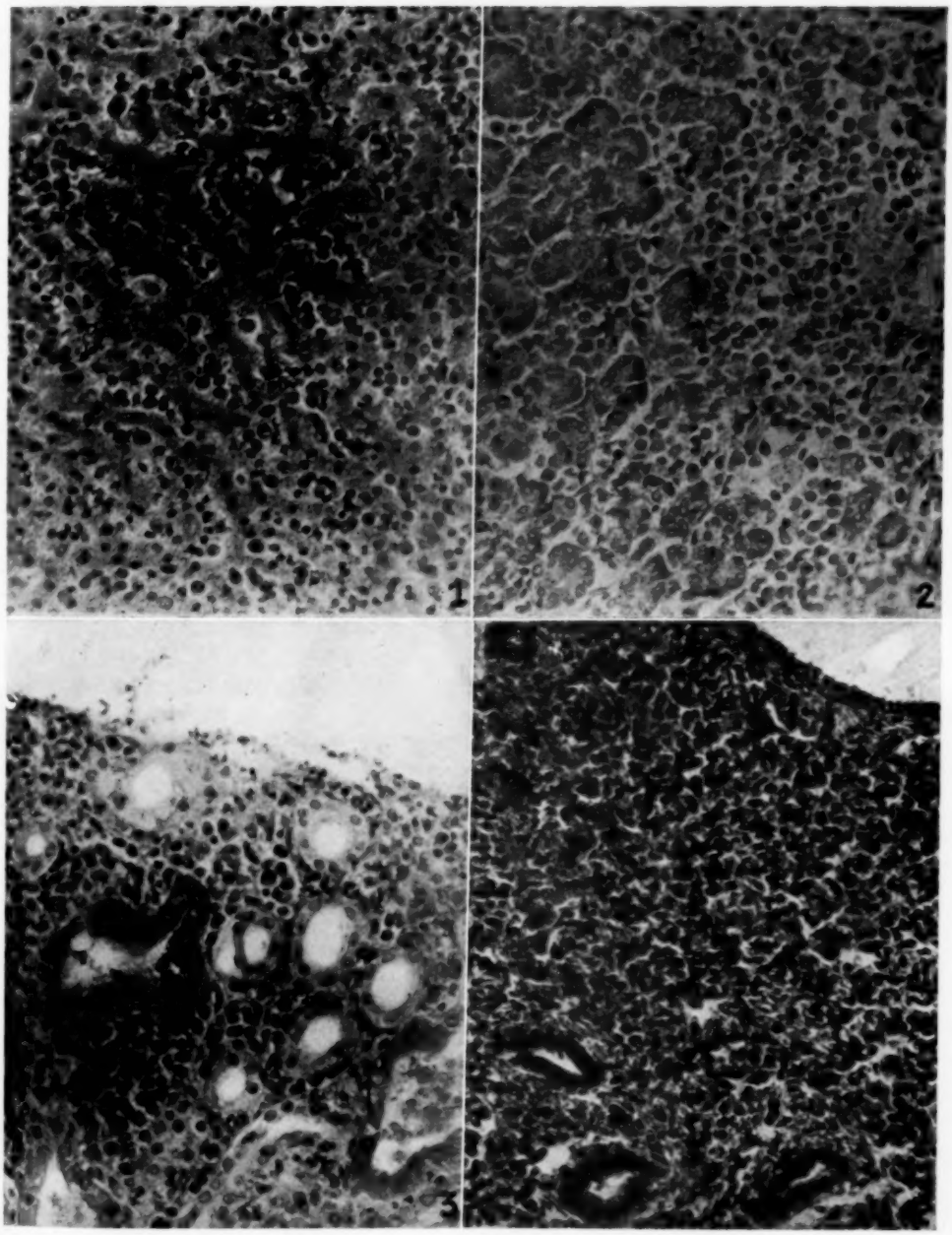

FIG. 3. No. 1. Blood capillaries of the liver packed with tumor cells. (× 230.)
No. 2. Neoplastic invasion of a pancreatic lobule. (× 230.)
No. 3. Edge of a tumor cell nodule in the renal cortex. (× 230.)
No. 4. Uterine endometrium heavily infiltrated by tumor cells. (× 230.)

spinal fluid was clear and showed no increase in pressure. The cerebrum was moderately edematous and on the cut surface showed multiple cystic spaces up to one centimeter in diameter. These contained a cloudy yellow fluid. The only green area found in the brain was in the choroid plexus of the left lateral ventricle.

The pituitary was replaced by a mass of green tumor tissue which measured 2.4 by 2.3 by 1.3 centimeters. The sphenoidal sinus and posterior ethmoidal air cells were filled with the tumor tissue. Both orbital cavities were invaded in the retro-ocular recesses by tumor tissue with partial destruction of the supra-orbital plates. The retropharyngeal canal was patent and a probe could be readily passed from the much enlarged sella to the pharyngeal mucosa.

On microscopic examination the tumor tissue was found to have a very wide distribution corresponding to the green and maroon areas described grossly. The tumor cell was a round or oval cell averaging from nine to twelve microns in diameter in the section. The nucleus was placed acentrically at the edge of the cell and showed a rather lightly staining chromatin material without radial distribution of the granules. The cytoplasm was quite plentiful and was clear. No eosinophilic or basophilic granules were present. The cells were constant in their appearance in all tissues. Eosinophilic and neutrophilic polynuclear cells were quite numerous. There were many pigment laden phagocytes present, especially in sections from the nodules which grossly had shown a green color. This pigment was phagocytized blood from obstructed capillaries and varied from recognizable red blood cells through amorphous masses to crystalline deposits.

The various tissues retained in part their specific structures but showed a diffuse or massive infiltration of tumor cells. The lymph nodes and spleen were extensively infiltrated by tumor cells but the lymph follicles persisted to some extent. The liver cells were atrophic due to the tumor cell invasion and anoxemia. The blood vessels throughout the body were filled with tumor cells indicating that a marked leukemia was present at the time of death.

The vacuoles found grossly in the brain showed few tumor cells about them and represented a simple liquefaction process. This necrosis was produced by the obstruction of many of the arterioles by tumor cells with resultant small localized anemic infarctions of the cerebral substance. The pituitary was almost completely destroyed by tumor tissue and it was only with difficulty that any trace of its original structure could be found. The pancreas in addition to small masses of tumor cells showed areas of endothelial phagocytes having a foamy appearance.

Autopsy summary: A chloroma was found involving the periosteum of the skull, ribs, sternum, and vertebral bodies (the long bones were not examined), the thoracic and abdominal lymphoid tissue, the thymus, lungs, pericardial sac, liver, spleen, pancreas, kidneys, dura, pituitary and choroid plexus of the left lateral ventricle. The tumor was in a leukemic phase with all the vessels showing an abundance of the tumor cells. There was marked anemia and a generalized edema with pitting of the ankles and feet, a fatty degeneration of the liver and kidneys, calcification of the costal cartilages with abnormal softening of the bone of the ribs, sternum, vertebral bodies, and to a lesser extent of the skull cap. The cerebral arterioles were thrombosed by tumor cells with multiple areas of liquefaction necrosis. The thyroid gland and adrenals were hypoplastic. There was a terminal bronchial pneumonia.

Discussion

Nine days before death the patient had a white blood count of 10,100 white blood cells with no recognizable cancer cells in the blood stream. At autopsy there was a marked leukemia, sufficient to cause thrombosis of the cerebral vessels. The examination of the eyes three days before death showed definite evidence of leukemia with thrombosis of the arterioles.

The complete destruction of the pituitary might well have been related to the calcium deficiency in the bones and increase in the cartilages. No roentgen-ray evidence of such a change was noted during the examination eight days before death.

Fixed sections of the tumor stained with Weigert's iron hematoxylin and eosin, Goodpasture's oxidase stain, and Wright's stain were examined by Dr. Raphiel Isaacs of the Simpson Memorial Institute at Ann Arbor and Dr. Carl V. Weller of the University of Michigan. Dr. Isaacs concluded that the tumor cell, which in no case showed oxidase granules, was of the lymphocytic series rather than of the myelocytic series, but might possibly be of the plasma cell type. Dr. Weller felt that no classification of the cell as to lymphocytic or myelocytic origin was justifiable and that the tumor cell was too primitive to indicate the potentialities of differentiation of its parent type.

The extensive deposits of blood pigment in various stages of phagocytization in the tumor nodules were responsible for the green discoloration of tissue which characterized the so-called chloroma. There was no evidence in our case that the tumor cells themselves had any relationship to the green pigmentation. There may have been a faulty production of hemoglobin or an increased destruction—which, we are not prepared to say—but the green color was due to phagocytosis of the red blood cells in the capillaries in the tumor nodules. Tumor nodules may uncommonly occur without any green color, and in the leukemic invasion of the organs there is no green pigmentation.

It is to be noted that the tumor affecting bone appeared upon only one side in every case, that side being the one where the nutrient vessels entered the bone.

Summary

A case is reported of chloroma in a 13 year old white female. The tumor was in an aleukemic phase nine days before death but was leukemic at death. There was a very extensive involvement of the cranium and body viscera. The tumor cell did not show the oxidase reaction.

Conclusion

1. Chloroma is a faulty designation as the green coloration is not specific of any one tumor cell type.
2. The green pigmentation is due to phagocytosis of the blood in the obstructed capillaries by the endothelial cells.
3. The tumor cell of chloroma is not necessarily myelocytic in origin.

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EDITORIAL

THE REPORTED INCREASE IN INSANITY AND FEEBLEMINDEDNESS

It has been frequently stated that an alarming increase is occurring in the numbers of the insane and of the feebleminded. This assumption has influenced many legislators in favor of optional or compulsory sterilization of the mentally afflicted as a means of limiting this increase. In May of 1934 the American Neurological Society appointed a committee to study the whole question of eugenical sterilization. This committee, working under a grant from the Carnegie Foundation, brought in its preliminary report in 1935. The full report has only recently been available in published form.[1] It contains a very interesting review of the data bearing upon this matter of the increasing frequency of insanity and feeblemindedness.

In previous studies great stress has been laid upon the rapid rise in the number of insane per 100,000 of population as indicating a great increase in mental disease. There exists, however, no adequate survey of the entire population and the rates quoted are based for the most part upon the number of hospitalized insane in the community. This number, however, can not be taken as a true index of the incidence of mental disease since it is very obviously influenced by the growing recognition on the part of the public of the desirability of commitment, by prevailing economic situations which may render commitment as opposed to the expense of home care more imperative, and by the availability of adequately equipped hospitals which diminishes the family resistance to institutional care for one of its members. The number of hospitalized insane no doubt bears some relation, modified by the above factors, to the total of living cases in the population, but a much less definite relation to fluctuations in incidence. A study of various states shows that where the level of public education is high and where well managed psychopathic institutions are provided the commitment rate is high whereas in states with a lower level of literacy and with few and poorly equipped mental hospitals the commitment rate is low.

It has been argued that the stress and strain of city life are potent factors in producing insanity, and the higher percentage of urban cases confined in institutions has been cited in support of this view. The explanation however, may be that the residents of cities are better informed as to the value of psychiatric care, that the necessary institutions are usually nearer at hand and that the home care of the insane is less feasible in crowded city living quarters than on farms.

[1] Eugenical Sterilization, Committee of the American Neurological Association for the Investigation of Eugenical Sterilization. New York, The Macmillan Company, 1936, page 211.

The committee made a special study of two relatively stable communities, the states of New York and Massachusetts, to see whether new data representing more accurately the fluctuations in true incidence of mental disease could be obtained. In both of these states there has been a well publicized campaign for mental hygiene for some years, and both are well provided with strategically placed mental hospitals. It was felt that a study of the admission rate (first admissions), as opposed to the number of inmates of hospitals, in these two states over a period of years might throw new light on the subject.

In the interpretation of the data the estimated increase in the population has been taken into account as well as the fact that the average age of the population is increasing. Also the age periods at which the various psychoses occur has been allowed for. Since paresis, for example, rarely occurs in those under thirty-five, the admission rate of paretics was calculated in relation to the quota of the population thirty-five or over. The lower age limit for manic depressive psychosis and for dementia precox was taken as fifteen; that for cerebral arteriosclerotic and senile dementias as fifty-five; and that for all psychoses combined as fifteen years. In Massachusetts the period studied was from 1920 to 1933, both inclusive; and in New York the years 1917 to 1934, both inclusive, were reviewed.

In Massachusetts the admission rate for all psychoses combined was 102.0 per 100,000 in 1920. In the ensuing years it fell as low as 94.0 and rose as high as 118.0 but for the last three years of the period studied the figures were 100.0, 98.5 and 102.0. Similar figures for all psychoses in the state of New York were 94.9 in 1917 and for the last three years of the period 106.0, 110.0 and 111.0. It is apparent that there has been at least no alarming increase in the admission rate for mental disease in these two large and relatively stable communities in the period investigated.

The analysis of the various groups of mental disorders as to their admission rates revealed some interesting facts. The combined group of manic depressive psychosis and dementia precox showed no significant change in admission rate during the period involved. The alcoholic psychoses in New York State showed a marked drop in admission rate during the first few years before and after prohibition was instituted, but thereafter the rate rose gradually to preprohibition levels. The admission rate of paretics showed a definite fall in both states. In New York State there was a definite and probably significant increase in the admission rate for cerebral arteriosclerotic and senile dementias.

The investigations of Winston [2] have shown that admission rates to mental hospitals, corrected for age, have shown no tendency to rise in recent years in England, Wales, Scotland, Australia, New Zealand or the Scandinavian countries. A definite increase was noted only in Germany.

[2] WINSTON, ELLEN: The assumed increase of mental disease, American Journal of Sociology, 1935, xl, No. 4.

Such data are of course not conclusive proof that insanity and feeble-mindedness are not increasing. Nothing but repeated surveys of the total population could be considered final. However the results of these studies are much stronger evidence against any great increase than has heretofore been put forward as indicating it.

The conclusion of the committee of the American Neurological Society on this point is of interest: "We do not believe that society needs to hurry into a program based on fear and propaganda. Although the problem of mental disease and defectives is enormous, there exists no new social or biological emergency."

REVIEWS

Modern Treatment and Formulary. By EDWARD A. MULLEN, P.D., M.D., F.A.C.S., Assistant Professor of Pharmacology and Physiology, Philadelphia College of Pharmacy and Science, Lieutenant Commander Medical Corps, U. S. Naval Reserve. 707 pages; 20 × 12 cm. F. A. Davis Company, Philadelphia. 1936. Price, $5.00.

This concise treatise on treatment is designed to be of ready use to the practitioner in his daily office and bedside work. The major portion of the volume is devoted to the materials of pharmacotherapy. The presentation of the physician's drug armamentarium is set forth in more than two thousand suggested prescriptions. The latest Pharmacopoeial nomenclature is employed. The arrangement of the materia medica is under the names of the diseases; cross references are frequent.

The appendix of the book considers many subjects in résumé form of special interest to the physician. Among these subjects are: formulae for fluid foods, diet tables, intravenous technic, dose tables and the antidotal treatment of various poisons.

The reviewer regrets that the table of antidotes is fragmentary. Doses of antidotes and specific information are not frequently included. The established nitrite-thiosulfate treatment of cyanide poisoning is omitted, most unfortunately the sodium formaldehydesulfoxylate treatment for bichloride of mercury poisoning has not been included and the treatment for barbiturate poisoning is naive and insufficient.

In the light of modern pharmacological opinion, i.e., writing a prescription based on the known action of one dependable drug, many of the prescriptions included seem archaic and bear the markings of the age of polypharmacy. Thus in one prescription, page 202, for enuresis the drugs rhus glabra, ergot, belladonna, triticum and jaborandi are prescribed.

Despite the above criticisms the author is to be congratulated on the compilation in such readily accessible manner of so much useful information pertinent to the daily work of the practitioner.

J. C. K., JR.

A Text-Book of Pharmacology and Therapeutics or *the Action of Drugs in Health and Disease.* By ARTHUR CUSHNY, M.A., M.D., LL.D., F.R.S. Eleventh Edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics and Director of the Pharmacological Laboratories, University of Michigan; and J. A. GUNN, M.A., M.D., D.Sc., F.R.C.P., Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, England. 808 pages; 23 × 15 cm. Lea and Febiger, Philadelphia. 1936. Price, $6.50.

Pharmacologists welcome again the revision of this widely used treatise on the action of drugs. Eleven revisions bespeak its usefulness in the fields of pharmacology and medicine. Although three years only have passed since the appearance of the last revision of this text, the rapid strides in the field of medication embraced by the new volume make its appearance timely.

The book is divided into an introduction and seven parts. Part I includes the action of inorganic substances; Part II embraces substances which are characterized chiefly by their local action; in Part III, the action of drugs after absorption is discussed; Part IV treats of anthelmintics; Part V is devoted to antiseptics and disinfectants; Part VI is concerned mainly with Chaulmoogra oil and the subjects of Part VII are vaccines, toxins and antitoxins.

With certain slight alterations the arrangement of the contents has not been changed greatly. Simpler substances, e.g. salts, have been placed nearer the front of the treatise and groups of drugs have been collected into larger classes.

Many of the subjects which were missing in the last edition are to be found in the present revision. Among these is a short résumé of the action of drugs on cells, an extension of the sections on liver therapy, arsphenamine, avertin, atabrine and carbarsone.

The modern treatment of cyanide and mercuric chloride poisoning is included, though the mechanism of the action of the later is not mentioned. The statement on page 428 that picrotoxin has not been employed in therapeutics in cases of collapse is questionable.

The style of the book is concise and lucid and its general printing, arrangement, excepting many of the structural formulas, is excellent.

The reviewer is of the opinion that this revision, like those in the past will continue to rank high among the textbooks in the English language.

J. C. K., Jr.

Chronic Indigestion. By C. J. Tidmarsh, M.A., M.D., F.R.C.P.(C). 143 pages; 14 × 20 cm. Longmans, Green and Company, New York. 1936. Price, $1.50.

The author's purpose in writing the book apparently seems to be threefold. He desires to educate the patient; to supplement the advice of the physician and to stress the need for coöperation between patient and physician. The information given is not intended to allow the patient to treat himself but rather to help him in carrying out instructions intelligently.

The book is written in elementary style and does not go over the heads of its lay audience. The approach through anatomy and physiology to causes, symptoms, diagnosis (investigation of case) and treatment gives the layman the accepted method of understanding disease processes. The limitation of its discussion to the type of indigestion associated with definite pain accounts for the author's ability to keep the size of his book within commendable limits.

It is indeed gratifying to see the emphatic indictment of the use of tobacco as an accessory factor in the production of peptic ulcer. It would seem, however, that other dogmatic statements are out of place in a book of this kind. Reference is made to such remarks as "ulcer pain is never present before breakfast" and "vomiting never occurs in the absence of pain." Moreover, in the discussion of cancer of the stomach the mere mention that "a person over 35 years of age who has not had previous attacks of indigestion and now complains of loss of appetite, etc., should be presumed to have cancer of the stomach until proved otherwise," may be enough to cause hysteria. It would be far more desirable in writing for laymen to suggest that such may be a possibility. The remarks about healing of ulcer are also somewhat misleading. One gets the impression that ulcers heal rather promptly (three to four weeks) whereas in the majority of cases, even under the best of conditions, actual healing is not consummated for months. Patients may as well know this and be resigned to months of coöperation in following out their treatment. The recommendation of sanitaria for ulcer cases is unusual though it may help to impress the patient with the necessity for readjustment of his habits and environment. The stress laid upon complete examination is commendable.

There are other minor criticisms but on the whole the author accomplishes his purpose. The book is concise and proves to be very readable.

S. M.

Keeping Your Child Normal. By BERNARD SACHS, M.D. 148 pages; 13.5 × 19 cm. Paul B. Hoeber, Inc., New York. 1936. Price, $1.50.

Out of many years of experience in dealing with the problems of childhood, Dr. Sachs has written this little book of mellow wisdom. It is the sort of book that should be read by every physician and layman who has to deal with children—and preferably read in the evening with a leisurely and thoughtful mind. By the same token it will probably be read by very few of the persons most in need of it, because it contains little that is spectacular, and because it offers no new theories to try out on the next little victim who comes along.

Throughout all the pages of his book, Dr. Sachs preaches the doctrine of common sense in handling children, and he repeatedly warns against a too eager acceptance of the latest psychological theories of child training. "A little respect for tradition and for the experience of the past is no obstacle to true progress." He shows vividly the harm that may be done to a perfectly normal child by subjecting him, for example, to the influence of a sexually minded psychoanalyst, or the damage done by "modern parents" who subscribe to the doctrine of "complete self-expression" for their youngsters.

Dr. Sachs misses very few of the many aspects of child psychology, and there are few that he does not enlighten with a pertinent comment. A multitude of topics such as: the responsibility of the father in the guiding of his children; the value of discipline in the very young; the effects of reading and movies; juvenile delinquency; the relative importance of heredity versus environment; the need of inculcating the old-fashioned virtues of consideration, honesty, and industry; the proper conduct of social service agencies and child guidance clinics are all touched on in this book.

The large section of the book, which is devoted to what the author terms "The Use and Abuses of Psychoanalysis," is essentially a biting criticism of psychoanalysis as it is practiced today. This chapter is well worth reading as the opinion of a sane and experienced psychiatrist on this particular subject, but the reviewer cannot see how it contributes very much to the discussion on "Keeping Your Child Normal."

C. H.

Tuberculosis in the Child and the Adult. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P. 611 pages; 16 × 23.5 cm. C. V. Mosby Company, St. Louis. 1934. Price, $8.50.

The author's wide experience and uncommonly sane clinical judgment have enabled him to produce a very valuable volume on tuberculosis in the child and in the adult. The modern concepts of the development of primary tuberculosis and of its later course have been fully presented. The subject of the relationships between allergy and resistance in tuberculosis is interestingly discussed. The author feels that allergy plays a large rôle in combating the infection. The visceral reflexes involved in the symptomatology of pulmonary disease receive full attention. Dr. Pottenger has long had a special interest in this subject. He is also among those who attribute considerable therapeutic value to tuberculin. In discussing the diagnostic use of tuberculin more might have been added as to the dangers of the subcutaneous test, and the advantages of the intracutaneous method might have been more strongly set forth. The discussions of the clinical aspects of the disease and of its treatment are excellent. The volume is richly illustrated with roentgenograms. Dr. Pottenger's book will be of great value to internists and pediatricians who feel the need of a modern one volume text on tuberculosis.

A. H. F.

COLLEGE NEWS NOTES

Life Member

Dr. W. E. Kendall of Oak Park, Ill., has become a Life Member of the College under date of December 14, 1936.

Gifts to the College Library

The College gratefully acknowledges receipt of the following gifts to the College Library of publications by its members:

Books

Dr. Lawrason Brown (Fellow), Saranac Lake, N. Y.—one autographed copy, "Rules for Recovery from Tuberculosis";
Dr. Walter Freeman (Fellow), Washington, D. C.—one autographed copy, "Neuropathology: The Anatomical Foundation of Nervous Diseases";
Dr. Solomon Katzenelbogen (Fellow), Baltimore, Md.—one autographed copy, "The Cerebrospinal Fluid and Its Relation to the Blood";
Dr. William C. Menninger (Fellow), Topeka, Kan.—one autographed copy, "Juvenile Paresis";
Dr. Anthony C. Cipollaro (Associate), New York, N. Y.—one autographed copy, "Skin Diseases in Children."

Reprints

Dr. Oscar W. Bethea (Fellow), New Orleans, La.—12 reprints;
Dr. Milton A. Bridges (Fellow), New York, N. Y.—3 reprints;
Dr. A. Allen Goldbloom (Fellow), New York, N. Y.—2 reprints;
Dr. H. Beckett Lang (Fellow), Brentwood, N. Y.—1 reprint;
Dr. John W. Shuman (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Virgil E. Simpson (Fellow), Louisville, Ky.—1 reprint;
Dr. Walter C. Swann (Fellow), Huntington, W. Va.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint.

Dr. Charles H. Cocke (Fellow), Asheville, N. C., was the orator for the annual meeting of the Jefferson County (Ky.) Medical Society, held during December in conjunction with and sponsored by the Louisville Tuberculosis Association.

Dr. Edgar F. Kiser (Fellow), Indianapolis, Ind., has been elected President of the Indianapolis Medical Society.

At the annual meeting of the Rensselaer County (N. Y.) Medical Society, Dr. Stephen H. Curtis (Fellow), Troy, was elected President for 1937.

Dr. Harold Swanberg (Fellow), Quincy, Ill., was reëlected Secretary-Treasurer of the Mississippi Valley Medical Society at its annual meeting in Quincy, Ill., during

November. Dr. Dan G. Stine (Fellow), Columbia, Mo., was elected to the Board of Directors for a two-year term for Missouri.

The Medical Association of Puerto Rico held its annual meeting in Santurce, P. R., December 18–20. Dr. O. Costa Mandry (Fellow) was President of the Committee on Arrangements. A paper on "Applied Therapeutics" by Dr. A. C. Morgan (Fellow), Philadelphia, was read by invitation. Other members contributing to the program were: Dr. Ramon M. Suarez (Fellow), "Comparative Effects of Crude and Purified Liver Extracts in the Anemia of Sprue Administered Intramuscularly and Intrasternally"; Dr. Enrique Koppisch (Associate), "Tissue Reactions in Diseases Caused by Filterable Viruses"; and Dr. Rafael Rodriguez Molina (Fellow), "Hematological Studies on Malaria in Puerto Rico."

Major General M. W. Ireland (Fellow) is President of the National Board of Medical Examiners of the United States. Among Fellows of the College who are members of this Board are Dr. Walter L. Bierring, Des Moines; Dr. Charles A. Elliott, Chicago; Dr. Reginald Fitz, Boston; Dr. Waller S. Leathers, Nashville, Tenn.; Dr. George W. McCoy, U. S. Public Health Service; Dr. William deB. MacNider, Chapel Hill, N. C.; Dr. Walter W. Palmer, New York City; Dr. Thomas Parran, Surgeon General, U. S. Public Health Service; Dr. O. H. Perry Pepper, Philadelphia; Dr. Charles R. Reynolds, Surgeon General, U. S. Army; Dr. P. S. Rossiter, Surgeon General, U. S. Navy; Dr. Harold Rypins, Albany, N. Y.; Dr. J. F. Siler (M.C.), U. S. Army; Dr. J. Gurney Taylor, Milwaukee, Wis.

Dr. Wilmar M. Allen (Fellow) has been appointed Director of the Hartford (Conn.) Hospital.

Dr. Herman M. Baker (Fellow), Evansville, Ind., has been made President-Elect of the Indiana State Medical Association for 1937.

Dr. James B. Collip (Fellow), Professor of Biochemistry, McGill University Faculty of Medicine, Montreal, will deliver a lecture on "The Significance of Recent Studies on the Anterior Pituitary and Related Glands," April 16, 1937, this being one of a series of lectures sponsored by the William Harvey Society of Tufts College Medical School, Boston.

The third annual symposium at Duke University School of Medicine, Durham, N. C., was held during October on diseases of the heart, circulation and kidneys. Fellows of the American College of Physicians included among the speakers were Drs. Warfield T. Longcope and Louis Hamman, Baltimore; Dr. Carl J. Wiggers, Cleveland; Dr. Charles C. Wolferth, Philadelphia; Dr. Frank N. Wilson, Ann Arbor; Dr. William deB. MacNider, Chapel Hill; Dr. James Edwin Wood, Jr., Charlottesville, Va.; Dr. William B. Porter, Richmond, Va.; Dr. Stewart R. Roberts, Atlanta; and Dr. Soma Weiss, Boston.

Dr. Charles E. Sears (Fellow), Portland, has been elected a Vice-President of the Oregon State Medical Society.

Dr. Walter F. Donaldson (Fellow), Pittsburgh, has been reëlected Secretary of the Medical Society of the State of Pennsylvania.

The bulk of an estimated estate of more than $200,000 has been bequeathed by the late Frances T. Kinsey to the University of Pennsylvania to support and develop the Gastro-Intestinal Clinic at the University Hospital, under the direction of Dr. Thomas Grier Miller (Fellow), or for such other activities in this field as he may desire.

Dr. Samuel B. Scholz, Jr. (Fellow), Philadelphia, has been elected a vice-president of the Association of Life Insurance Medical Directors of America.

Dr. Henry W. F. Woltman (Fellow), Rochester, Minn., has been elected President of the Central Neuropsychiatric Association.

Dr. Edward A. Strecker (Fellow), Philadelphia, has been appointed a member of the advisory committee of the Friedsam Foundation, in connection with its program of research in child neurology. The research program will include studies of (1) organic and functional diseases of the nervous system in children; (2) neuroses and psychoses in early life; and, (3) social personality and home problems. The program will be carried on through grants and scholarships to research workers throughout the world. Only original work that promises to be fruitful of results will be considered. The applicant must state specifically the problem under investigation and the methods to be pursued. The Council of the Foundation will publish the results from year to year.

Dr. Herbert L. Bryans (Fellow), Pensacola, Fla., has been elected a Vice-President of the Gulf Coast Clinical Society.

Dr. Gordon B. Myers (Associate), Detroit, has been appointed Professor and acting head of the Department of Medicine of Wayne University College of Medicine. Dr. Hugo A. Freund (Fellow), Detroit, has been appointed Professor of Clinical Medicine.

Dr. Eugene M. Landis (Fellow), Philadelphia, gave the second Harvey Society Lecture at the New York Academy of Medicine, November 19, on "The Passage of Fluid Through the Capillary Wall."

Dr. George R. Minot (Fellow), Professor of Medicine, Harvard University Medical School, Boston, delivered the sixth Walter M. Brickner Lecture at the Hospital for Joint Diseases, New York City, November 19, on "Anemia: Etiology, Diagnosis and Treatment."

Dr. Soma Weiss (Fellow), Boston, was guest speaker at the joint meeting of the Cincinnati Academy of Medicine and the Heart Council of Greater Cincinnati,

recently, his subject being "The Relation of the Cardiovascular System to the Nervous System."

As a memorial to the late Dr. James M. Anders (Master), Philadelphia, the Philadelphia County Medical Society devoted its meeting of November 25 to the observance of the annual Pennsylvania Health Day, a movement primarily sponsored in its beginning by Dr. Anders. Dr. George E. Pfahler (Fellow), Philadelphia, delivered a tribute to Dr. Anders, and Dr. Baldwin L. Keyes (Associate), Philadelphia, presented a report of the Society's noise abatement committee, whose work was one of the last activities sponsored by Dr. Anders before his death last August.

Dr. Elliott P. Joslin (Fellow), Boston, is President of the Interstate Post-Graduate Medical Association.

Dr. Byrl R. Kirklin (Fellow), Rochester, Minn., is President-Elect of the American Roentgen-Ray Society. Dr. Charles A. Waters (Fellow), Baltimore, now occupies the Presidency.

Dr. John H. Wyckoff (Fellow), New York City, recently assisted in the presentation of a symposium on sterilization before the section of obstetrics and gynecology of the New York Academy of Medicine.

Dr. Ray M. Balyeat (Fellow), Oklahoma City, and Dr. Hal M. Davison (Fellow), Atlanta, were guest speakers on the program of a clinical congress held during the past autumn by the Chattanooga and Hamilton County (Tennessee) Medical Society.

In honor of his thirty-three years of service to organized medicine, Dr. Rock Sleyster (Fellow and Governor for Wisconsin), Wauwatosa, Wis., was tendered a dinner by the Medical Society of Milwaukee County at the Wisconsin Club, Milwaukee, on November 14. Dr. Arthur J. Patek (Fellow), Milwaukee, was toastmaster. Dr. J. Gurney Taylor (Fellow), Milwaukee, was one of those delivering an address. Dr. Sleyster is Chairman of the Board of Trustees of the American Medical Association. In 1903 he became Secretary of the Calumet County Medical Society, holding the post for six years. In 1910 he was elected Assistant Secretary of the State Medical Society of Wisconsin and its Secretary in 1914, holding this appointment until 1923. In 1924 he was elected President of the State Society, and since 1925 he has been its Treasurer. From 1918 to 1923 Dr. Sleyster was Editor of the Wisconsin Medical Journal. He served as delegate to the American Medical Association from 1915 to 1926, and for the last four years of that period he was Vice Speaker of the House of Delegates. He has been a Trustee since 1926 and Chairman of the Board since 1935. He graduated from the University of Illinois College of Medicine, Chicago, 1902. At present he is medical director of the Milwaukee Sanitarium.

Dr. Francis E. Harrington (Fellow), Minneapolis, has been reëlected Secretary of the International Society of Medical Health Officers.

The Alumni Association of the College of Medical Evangelists, Los Angeles, held its third annual postgraduate assembly in Los Angeles, December 6. Among the speakers were: Dr. James F. Churchill (Fellow and Governor for Southern California), San Diego, "A Discussion of Cardiac Drugs and Their Uses"; Dr. Alvin G. Foord (Fellow), Associate Professor of Pathology, University of Southern California School of Medicine, "Laboratory Diagnosis for the General Practitioner"; and Dr. William J. Kerr (Fellow and Regent), Professor of Medicine, University of California Medical School, "Obesity and Its Complications."

Dr. William B. Castle (Fellow), Boston, addressed the graduate teaching clinic of the Central Maine General Hospital, Lewiston, Maine, December 18, on "Development of the Knowledge of Vitamin Deficiency Diseases."

Dr. Bernard Fantus (Fellow), Chicago, was a guest speaker on the program of the joint meeting of the Wayne County Medical Society and the Detroit Retail Druggists Association, December 7, when the newly revised Pharmacopoeia and the National Formulary were discussed.

Dr. William M. Donald (Fellow), Professor and Head of the Department of Medicine, Wayne University College of Medicine, Detroit, was a guest of honor at a joint meeting of the staff of the Receiving Hospital and the medical faculty recently, in recognition of his many years of service to both institutions. Dr. Donald is seventy-six years of age and has been a member of the teaching staff of his alma mater since 1889. He was President of the Wayne County Medical Society in 1922 and has been a Fellow of the American College of Physicians since 1917.

Dr. Sydney R. Miller (Fellow and Regent), Baltimore, and Dr. Leander A. Riely (Fellow and Governor for Oklahoma), Oklahoma City, have been elected Vice-Presidents of the Southern Medical Association.

Dr. Henry A. Luce (Fellow), Detroit, was one of the speakers on a panel discussion of the relation of social security to the practice of medicine, sponsored by the medical economics committee of the Wayne County Medical Society and the Michigan State Medical Society, December 9.

Dr. James H. Black (Fellow) has been promoted to Professor of Clinical Medicine (Allergy) on the Faculty of Baylor University School of Medicine, Dallas.

Dr. George R. Minot (Fellow), Boston, on December 1 at the Waldorf-Astoria Hotel, New York City, received the annual award for research in the field of nutrition leading to the prevention of disease and the advancement of health, the award being made by the Associated Grocery Manufacturers Association of America.

Dr. Hugh S. Cumming (Fellow), formerly Surgeon General of the U. S. Public Health Service, was Chairman of the local Committee on Arrangements for the

second National Conference on College Hygiene, held in Washington December 28 to 31.

Dr. Cumming was presented with the Marcellus Hartley Gold Medal " for eminence in the application of science to the public welfare " at the annual meeting of the National Academy of Sciences, in Chicago during November.

Dr. Earl B. McKinley (Fellow), Dean and Professor of Bacteriology, George Washington University School of Medicine, is on sabbatical leave, dating January 1, for a trip to the Orient, where he will conduct research on leprosy under the auspices of the American Leprosy Foundation, formerly the Leonard Wood Memorial. Dr. McKinley will later continue his travels around the world, gathering material concerning the geographic distribution of disease for inclusion in a new book now in preparation, " A Cartography of Disease."

Dr. Charles Franklin Craig (Fellow), Professor of Tropical Medicine, Tulane University of Louisiana School of Medicine, New Orleans, delivered the annual oration of the Smith-Reed-Russell Society, George Washington University School of Medicine, Washington, D. C., on " Factors Influencing the Transmission of Malaria," during November.

Dr. James S. McLester (Fellow and ex-Regent), Birmingham, Ala., has been appointed Professor of Medicine at the University of Alabama School of Medicine. Dr. Edgar Gilmore Givhan, Jr. (Associate) and Dr. James B. McLester (Associate) have been appointed Associate Clinical Professors of Medicine.

Dr. Thomas B. Magath (Fellow), Rochester, Minn., has retired as Editor of the " American Journal of Clinical Pathology," after serving six years. Dr. Robert A. Kilduffe of Atlantic City, N. J., succeeds Dr. Magath as Editor.

Dr. Charles A. Doan (Fellow), Professor of Medicine and Medical Research, Ohio State University College of Medicine, has been appointed Chairman of the Department. Dr. George T. Harding, III (Fellow), is Assistant Clinical Professor of Medicine (Psychiatry), and Lt. Col. Frank H. Dixon (Fellow), Medical Corps, U. S. Army, is Professor of Military Science.

Dr. Lee Rice (Fellow), San Antonio, Tex., is President of the Texas Club of Internal Medicine.

Dr. Porter P. Vinson (Fellow), Rochester, Minn., has been appointed Professor and Head of the Department of Bronchoscopy, Esophagoscopy and Gastroscopy at the Medical College of Virginia, Richmond. He will also be in charge of chronic pulmonary diseases at the Memorial Hospital.

Dr. David P. Barr (Fellow and Regent), St. Louis, has been elected President of the Central Society for Clinical Research.

Dr. Charles H. McEnerney (Fellow), Washington, D. C., has been reëlected Secretary of the American Society for the Study of Arthritis.

Dr. Leroy S. Peters (Fellow), Albuquerque, N. M., has been made President-Elect of the southwestern Medical Association. Dr. Howell S. Randolph (Fellow), Phoenix, Ariz., and Dr. Orville E. Egbert (Fellow), El Paso, Tex., have been elected Vice-President and Secretary respectively.

Dr. N. M. Marr (Associate), St. Petersburg, Fla., has been elected President of the Pinellas County (Florida) Medical Society.

Dr. A. Clayton McCarty (Fellow), Louisville, Ky., has been elected President of the Jefferson County (Kentucky) Medical Society.

Dr. George A. Gray (Associate), Abilene, Tex., has been appointed Director of the Nolan County Health Unit.

Dr. R. M. Wylie (Fellow), Huntington, W. Va., has been elected President of the Cabell County (West Virginia) Medical Society.

OBITUARIES

OSKAR KLOTZ, M.B., M.D., F.R.C.P.(C)., F.A.C.P., F.R.S.C., 1878–1936

THOSE who knew Oskar Klotz well find it difficult to express to others their full appreciation of the man. Widely known as a research worker and teacher, studying, investigating, directing and advising, with his activities spread over three continents, he became an authority in many of the departments of his chosen field of pathology. To his associates he was a great source of inspiration. With a remarkable ability to apply his knowledge whether from his own or other source, he was peculiarly fitted for the study of special problems in the origin of disease, its manifestations and its effects. The appended outline of his preparatory and postgraduate education, his various appointments, his memberships and offices held in national and international societies bespeak his wide variety of interests, the recognition by his fellow workers of his ability and genius and the high esteem in which he was held by men with whom he came in contact in his many spheres of activity.

Many tributes have been paid to him and to his work perhaps none more speaking than that from the Sisters of Mercy in Pittsburgh, who learning of his death sent the message that they could never forget the aid he gave them in the development of their hospital. Night after night was given freely to them during his busy life in that city, after days of labor in the University and its laboratories.

His contributions to medical literature number over one hundred titles. His studies of disease of the circulatory system made him an international authority. In tropical diseases he became one of the leaders. In his University he developed departments which proved him a great administrator. His library contained all that was important of the new and the most valuable of the old. His studies, his writings, his reading gave evidence that he appreciated the historical approach to questions under investigation. His grasp of any subject was wide; his early death means the loss of many important contributions to historical medicine.

His papers based on such reading were written in faultless English, and in such a style as to make him one of our outstanding essayists. I have frequently found myself looking upon him with Welch and Warthin as the three admirable, lovable pathologists of our time.

He was born in Ontario of Danish stock from Kiel, Holstein. His father was Chief Astronomer of the Dominion Observatories, a graduate of the University of Toronto and of Michigan, whose achievements won world wide fame. Two brothers, one of whom pre-deceased him, also graduated in medicine at the University of Toronto.

The funeral on November 15 was from Osler Hall of the Academy of Medicine, Toronto, where he presided last year. The service was conducted by Dr. H. J. Cody, President of his University, and by Sir Robert Falconer, President Emeritus, in the presence of the Lieutenant Governor of the Province, representatives of the National Research Council at Ottawa, his colleagues in Pittsburgh and The University of Toronto, most of the Fellows of the Academy, and many of his students and friends.

To his wife, Stella M. Scovill, who survives him, this College extends its sincerest sympathy.

Oskar Klotz, M.B., M.D., C.M. Born, January 21, 1878, at Preston, Ont. Attended Ottawa Collegiate Institute and the University of Toronto (M.B., 1902); M.D., C.M., Faculty of Medicine, McGill University, 1906. Postgraduate study at the University of Bonn, Bonn, Germany, 1905; University of Prague, Prague, Bohemia, 1905; University of Freiburg, Freiburg, Germany, 1908; University of Marburg, Marburg, Germany, 1914; house physician, Ottawa General Hospital, 1902–03; Governor's Fellow in Pathology, McGill University, 1903–05; Fellow in Pathology, Rockefeller Institute, 1905–06; demonstrator in Pathology and Bacteriology, McGill University, 1905–07; assistant pathologist, Royal Victoria Hospital, 1905–10; pathologist, Maternity and Alexandra Hospitals, Montreal, 1905–10; lecturer in Pathology, McGill University, 1907–10; professor of Pathology and Bacteriology, University of Pittsburgh, 1910–20; director, Magee Pathology Laboratory, Pittsburgh, 1910–20; professor of Pathology, Faculdade de Medicine, Sao Paulo, Brazil, 1920–23; professor of Pathology and Bacteriology, University of Toronto, 1923 to date; director of pathology laboratories, Toronto General Hospital, 1923 to date; consulting pathologist, Hospital for Sick Children, 1923 to date; at one time a special member, Yellow Fever Commission, Rockefeller Foundation; member, Zeta Psi, Nu Sigma Nu and Alpha Omega Alpha Fraternities; past president of American Association of Pathologists and Bacteriologists, International Association of Medical Museums, Academy of Medicine of Toronto and Society for Experimental Pathology; member of council of National Research Council of Canada, American Association of the History of Medicine, Ontario Branch of St. John's Ambulance Association and the Royal Canadian Institute of Toronto; member, Toronto Health League, Ontario Medical Association, Canadian Medical Association, Royal Society of Canada, Royal College of Physicians and Surgeons of Canada, Cancer Commission and chairman of subcommittee on Cancer Research (Ontario), International Association of Geographical Pathology (joint chairman for Canada), International Society for the History of Medicine, Medical Advisory Committee in conjunction with Ontario Crippled Children, Pathological Society of Great Britain and Ireland, Society for Experimental Biology and Medicine, Society for Tropical Diseases, American Society of Parasitologists, American Society of Tropical Medicine, Association of American Physicians and the American College of Physicians (Fellow, 1924).

JABEZ H. ELLIOTT, M.B., F.A.C.P.,
Governor for Ontario

DR. WILLIAMS McKIM MARRIOTT

Dr. Williams McKim Marriott, Fellow, died in San Francisco, November 11, 1936. He had only recently come to San Francisco from Washington University Medical School to assume the duties of Professor of Research Medicine and Dean of the Medical Faculty of the University of California.

Dr. Marriott was born in Baltimore, Md., March 5, 1885. He received his B.S. degree from the University of North Carolina, 1904, and the degree of M.D. from Cornell University in 1910. He served as Assistant in Biochemistry in Cornell University from 1904 to 1907 and Instructor in Biological Chemistry, Washington University, 1910 to 1914. In 1914 he went to the Johns Hopkins Medical School as Instructor and Associate in Pediatrics, remaining until 1917, when he returned to Washington University, St. Louis, as Professor of Pediatrics, which position he held until July 1936, when he came to San Francisco. From 1923 until his resignation in 1936, he was Dean of the Medical Faculty of Washington University. As Professor of Pediatrics he became Pediatrician in Chief, Barnes Hospital, St. Louis Maternity Hospital and Washington University Clinics. He also held the title of Physician in Chief of St. Louis Children's Hospital.

During his academic career he was honored by the following lectureships: In 1920, Harvey Society Lecturer, New York; 1921, Packard Lecturer, Philadelphia; 1925, Lecturer, Chicago Institute of Medicine; 1927, Annual Lecturer, San Diego Academy of Medicine; 1932, Visiting Lecturer, University of California Medical School, and Lecturer, California Academy of Medicine, San Francisco.

The following list of society memberships and offices indicates the breadth of his medical interests as well as the recognition which his position in the profession merited: Fellow of the American College of Physicians; Regent from 1926 to 1929, Vice-President, 1929 to 1930. Fellow of the American Medical Association, member of the Council on Pharmacy and Chemistry and member of Foods Committee. Member of the Council American Pediatric Society. President of the St. Louis Pediatric Society. Member of Council American Society of Clinical Investigation. Association of American Physicians, American Society of Biological Chemists, American Association for the Advancement of Science, Society of Experimental Biology and Medicine, Harvey Society of New York (Honorary Member), American Academy of Pediatrics, Southern Medical Association, Chairman of the Sections on Medical Education and on Pediatrics.

He was a member of the Phi Beta Kappa and Alpha Omega Alpha honorary societies and served on the Editorial Boards of the *American Journal of Diseases of Children, American Heart Journal* and the *Journal of Clinical Investigation.*

Dr. Marriott's contributions to medical and biological chemical literature were prolific and could not very well be mentioned here, including, as they do, two books, one concerning the relationship of biological chemistry to medical practice, and one on Infant Nutrition. Sections dealing with Pediatrics, in four books and over 80 contributions in the form of articles on biological chemistry and pediatrics.

With this remarkable background, an outstanding figure in American Medicine, Dr. Marriott came to California to devote his time and energy

to research medicine and to the Deanship of the University of California Medical School. Before he was well settled in his new environment, his health became impaired by a chronic appendiceal abscess, which was treated surgically, but a blood stream infection ensued, eventually causing his death.

In Dr. Marriott's death the American College of Physicians has lost one of its distinguished and loyal members. We in California have lost a warm friend and fellow worker, whose life with us was all too brief.

ERNEST H. FALCONER,
Governor for Northern California

DR. WILLIS FASTNACHT MANGES

Willis Fastnacht Manges, M.D., D.Sc., was born in Luthersburg, Clearfield County, Pa., on December 4, 1876, and died in the Jefferson Medical College Hospital, Philadelphia, on November 24, 1936, of coronary thrombosis after a mercifully brief illness.

Dr. Manges attended Gettysburg College, Gettysburg, Pa., and the Philadelphia College of Pharmacy before entering the Jefferson Medical College from which institution he received his M.D. degree in 1903.

After completing his internship in the hospital of the Jefferson Medical College, Dr. Manges became actively associated with the Department of Roentgenology of the same College and Hospital, and in this Department he spent the greater part of his professional life in helpful, progressive work, research, study and in teaching.

Dr. Manges entered the field of Roentgenology in the pioneer period of that branch of medical science and lived to become one of its foremost authorities. Dr. Manges was fortunate, early in his professional career, to be intimately associated with such masters of medical science as W. W. Keen, J. Chalmers Da Costa, George E. de Schweinitz, Chevalier Jackson, Thomas McCrae and other like minded men of medicine who possessed, in addition to their medical knowledge, inspiring and stimulating personalities and who were never content with superficialities, but who sought and encouraged others to seek ultimate truth.

When the World War came, Dr. Manges felt it to be his duty to abandon a lucrative and interesting practice, an assured professional and social position and, far more important and difficult for him, to leave his young wife and baby for the uncertainties and vicissitudes of army medical life. Dr. Manges established, for the medical department of the Army, an efficient training school for roentgenologists at Camp Greenleaf, Fort Oglethorpe, Ga., that commanded the respect and admiration of the medical world. Many medical officers assigned for duty in the school for roentgenologists received from Dr. Manges not only excellent technical training but inspiration for making roentgenology a life work.

After the war the intimate association of Dr. Manges with Dr. Chevalier Jackson's epoch making studies of the abnormalities and disorders of the air

passages brought about Dr. Manges' outstanding contribution in this field, namely, a practical method of detecting the presence of non-opaque foreign bodies in the lower air passages.

In 1928 Dr. Manges was made Professor of Roentgenology at the Jefferson Medical College in well deserved recognition of the years of altruistic service rendered the medical school in giving inspiring instruction to both undergraduate and graduate students.

Dr. Manges was elected to Fellowship in the American College of Physicians in 1930 for, unlike many specialists in medicine, Dr. Manges was a skilled and understanding physician. His specialty was roentgenology and he limited his actual practice to this field of endeavor but, fortunately for his patients, for his colleagues and for his students, Dr. Manges held an active interest in clinical medicine and its problems. Modest to the degree of self effacement, Dr. Manges was time and again advanced by the unanimous vote of his professional colleagues to positions of honor in the profession.

He was President of the Philadelphia Roentgen Ray Society as well as Secretary, and, later, President of the American Roentgenological Society, and was active and interested in every association that he felt was helpful for the common good of the medical profession.

Willis Manges possessed, by virtue of fortunate heredity and entirely natural characteristics, an unusually attractive, admirable and lovable nature. He was unselfish, generous, and interested in helping others. Charitable to the faults and weaknesses of others, he maintained the highest standards of living and thinking in his own life, and commanded the respect and admiration of all who came in contact with him or with his work.

Dr. Manges is survived by his widow, who was Marie Elizabeth Bosley of Baltimore, and two sons, Willis E. and William Bosley. The College has lost a loyal, altruistic and helpful Fellow; the world, a kind, skilled and considerate physician, but no mere words can begin to express what the passing of Dr. Manges means to those near and dear to him. One can, however, be thankful that as long as the sons of Dr. Manges live, or their descendants, the qualities and characteristics that he so nobly exampled cannot be lost to the world.

E. J. G. Beardsley, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. MATTHEW A. DeLANEY

Brigadier General Matthew A. DeLaney (Fellow) of the Army Medical Corps Retired, who served as White House physician during the Taft Administration, died November 1, 1936, at Walter Reed General Hospital, Washington, D. C. He had been a patient at that hospital for about two months.

From 1931 until his retirement, General DeLaney was one of the As-

sistant Surgeons General. His last tour of duty was in command of the Medical Field Service School at Carlisle Barracks, Pennsylvania.

Less than a month after the United States entered the World War General DeLaney went to France to command the Pennsylvania Base Hospital No. 10. Early in 1918 he was appointed Liaison Officer to the British War Office, London.

A native of Waymart, Wayne County, Pennsylvania, where he was born March 6, 1874, General DeLaney was graduated from Pennsylvania Normal School and obtained his medical degree from the University of Pennsylvania in 1898. In 1902 he was graduated from the Army Medical School.

General DeLaney had also taken a course at the University of Vienna in 1913–14, and held a Certificate of Public Health from Harvard University. Dickinson College, Pennsylvania, last year made him an honorary doctor of science.

General DeLaney served in the Philippine Insurrection. He was White House Physician from 1909 to 1913. He served on the Mexican Border in 1916. When the World War was ended he became Executive Officer in the Office of the Surgeon General. In 1921 he was named Surgeon of the Field Artillery School at Fort Sill, Oklahoma, and in 1927 was ordered to assume the same duties at Camp Devens, Massachusetts. The following year be became medical adviser in public health and sanitation; first, to Henry Stimson, and then to Dwight W. Davis, who were in turn Governors General of the Philippines. In 1931 General DeLaney was ordered to Command Carlisle Barracks, his last station before retirement.

In addition to his being a Fellow of the American College of Physicians, he was a member of the American Public Health Association, a Fellow of the American Medical Association and of the American College of Surgeons. He contributed many articles to medical journals. Military honors accorded General DeLaney include the Distinguished Service Medal from the United States and the Order of St. Michael and St. George of Great Britain. Field Marshal Douglas Haig mentioned him in dispatches for " gallantry on the field." He was a member of the Order of St. Lazare of Jerusalem.

He belonged to the Metropolitan, Chevy Chase and Army and Navy Clubs of Washington, and the Army and Navy and Polo Clubs of Manila.

Surviving General DeLaney is his wife, Mrs. Elizabeth V. DeLaney, who makes her home in Washington.

CAPTAIN OWEN J. MINK

Captain Owen J. Mink, Medical Corps, U. S. Navy, the Assistant Chief of the Bureau of Medicine and Surgery, died suddenly at his home at Chevy Chase, Maryland, on October 21. Captain Mink was born at Pectone, Illinois, April 26, 1879, so was 57 years of age at the time of his death. He graduated from the Medical School of the University of Michigan in 1903 and was appointed Assistant Surgeon in the Navy June 7, 1904. His

home then was at Wheaton, Illinois. He was promoted Passed Assistant Surgeon June 7, 1907, Surgeon August 29, 1916, Commander July 1, 1918, and Captain, Medical Corps, October 2, 1925.

His first duty was at the Naval Hospital at Philadelphia, following which he received a postgraduate course of instruction in naval medicine at the U. S. Naval Medical School, completing this postgraduate course in the spring of 1905.

The types of duty performed by Captain Mink were of a most varied character and he held many important posts both afloat and ashore. In 1910 he was a member of the board to study and report upon the causes and prevention of typhoid fever in the Navy and he was a pioneer in the movement to introduce typhoid vaccination in the Navy. After this he served on the U. S. S. West Virginia, then a member of the famous armoured cruiser squadron. During the World War he was on duty at the Naval Training Station, Great Lakes, Illinois. After the war he served as Executive Officer of the U. S. Naval Hospital, Great Lakes, Illinois, and as Senior Medical Officer in Samoa and later as Senior Medical Officer in the Virgin Islands and Commanding Officer of the Naval Hospital at Saint Thomas. He then served as Commanding Officer of the Naval Hospital at Canacao, P. I.

From 1931 to 1933 he was Chief of the Division of Preventive Medicine in the Bureau of Medicine and Surgery. He was appointed Assistant Chief of the Bureau of Medicine and Surgery June 26, 1933.

Captain Mink was an outstanding medical officer of the United States Navy and was particularly distinguished in the fields of bacteriology and preventive medicine. Few men in this country surpassed him in point of knowledge of preventive medicine and public health, particularly in respect to the simple and homely common sense with which he applied this knowledge to the problems of disease prevention. The editor of the Journal of the Royal Army Medical Service quite recently in requesting permission to reprint an article on disease prevention written by Captain Mink, commented on its great value and the many practical features which it contained.

Captain Mink had a most likeable personality. Pleasant, sincere and unaffected, everyone who came in contact with him loved and admired him. He was very fond of flowers and was an ardent amateur gardener. Captain Mink is survived by his wife and three children. His death is a real loss not only to his family and friends but to the Medical Corps and the Naval Service.

P. S. Rossiter, M.D., F.A.C.P.,
Surgeon General, U. S. Navy

DR. THOMAS CRAIG REDFERN

Dr. Thomas Craig Redfern (Fellow), Winston-Salem, N. C., was born in Chesterfield County, S. C., July 31, 1892. He received his academic training at Clemson College, graduating with the degree of B.S. in 1912, and receiving his M.D. in 1916 from the Long Island College Hospital. After serving his internship there, he was for two years assistant surgeon in the United States Medical Corps, followed by a residency in medicine in Barnes Hospital, St. Louis.

He became medical director of the City Memorial Hospital, Winston-Salem, N. C., in 1920, and Chief of the medical service of that hospital from 1924 to 1931. He was likewise Chief of the Medical Service of the North Carolina Baptist Hospital from 1923 to 1931. From 1924 on, Dr. Redfern became an outstanding internist in his community; and besides serving on the staffs of the two hospitals mentioned, was a member of the Governing Board of the Forsyth County Tuberculosis Sanatorium, former President of the Forsyth County Medical Society, and a member of the North Carolina State Medical Society and of the Southern Medical Association, and a Fellow of the American Medical Association, as well as of the American College of Physicians. He was a former member of the Rotary Club and a member of the First Presbyterian Church.

August 15, 1936, he had a coronary thrombosis, succeeded by embolic phenomena, which caused his death from myocardial failure nine weeks later.

Dr. Redfern was a leader in his chosen field in his city, always studious, an original thinker, and a man of lovable character. He is survived by his widow and a son and daughter.

CHARLES H. COCKE, M.D., F.A.C.P.,
Governor for North Carolina

DR. THOMAS DEWITT GORDON

Thomas Dewitt Gordon (Fellow), of Grand Rapids, Michigan, died November 20, 1936, of coronary disease, aged 56.

Dr. Gordon was born in Maxwell, Ontario, on November 1, 1880. Graduating from the University of Michigan Medical School in 1909, he came to Grand Rapids to practice in 1911 directly from the University Hospital where he had been first assistant in Internal Medicine.

Dr. Gordon early offered his services to his country in the World War, and with the rank of Captain, organized and took over-seas Ambulance Unit Number 339. Detached over-seas, he became Chief Sanitary Officer of the 85th Division. Returning from the war he again took up his general practice, but soon determined to limit his work entirely to pediatrics in which he was much interested and for which he prepared by postgraduate work both in this country and abroad. In this special work for which he was so well suited, he developed an enviable reputation throughout the state.

Markedly competent and well trained, with a pleasing personality, he was much beloved and appreciated by his patients and his professional brothers. A forceful speaker, with a teacher's ability to handle his subject, he added much to professional discussion and was always in demand for talks on his chosen specialty.

The disease from which he died manifested itself two years earlier and compelled a prolonged absence from his work. He bore his affliction with great philosophy. Some six months before he died he thought himself sufficiently recovered to take a few months postgraduate work and return to practice. Within a few weeks of his return he was again going at full tilt, as was his custom, but the demands of practice soon resulted in a return of symptoms.

Dr. Gordon was an active member of the Blodgett Hospital Staff, an ex-president of the Kent County Medical Society, and a member of various pediatric societies. He had been a member of the American College of Physicians since 1919. Lovable, conscientious, always dependable, the profession has lost a valued member, a wise councillor and friend.

BURTON R. CORBUS, M.D., F.A.C.P.,
Grand Rapids, Mich.

DR. ARTHUR STERN

Dr. Arthur Stern (Fellow), Elizabeth, N. J., died suddenly November 28, 1936, of coronary thrombosis; aged, 68 years.

Dr. Stern was born in Geseke, Westphalia, Germany, in 1868. He received both his preliminary and medical education in his native Germany, but did not practice medicine there. After graduating from the Friedrich-Wilhelms University, and after passing his State Board examination at Munich, he joined the Hamburg-American Steamship Line as ship surgeon, and made five trips in that capacity across the Atlantic. In 1892, he came to Elizabeth, N. J., and began the practice of medicine and surgery. His fame grew sufficiently to justify his specializing in Pediatrics, which he pursued until his death. At the time of his death he held many responsible hospital positions. He was Senior Attending Physician at the Elizabeth General Hospital and Senior Attending Pediatrician at the St. Elizabeth Hospital, both of Elizabeth, N. J.

Dr. Stern became a Fellow of the College on January 30, 1920. He had been a president of the Union County Medical Society and a vice-president of the New Jersey Pediatric Society. He was a Fellow of the New York Academy of Medicine, the American Medical Association and a member of the American Child Hygiene Association. He had published numerous articles.

In Dr. Stern's death, the people of Elizabeth, the profession and the College, have suffered an irreparable loss.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey

DR. JACOB C. ATWELL

Following an illness of but two days, Dr. Jacob Clinton Atwell (Fellow) of Butler, Pennsylvania, died on November 2, 1936, of pneumonia.

Dr. Atwell was born in Boyers, Butler County, March 25, 1874. He received his early education in the local public schools and later attended the Slippery Rock State Normal School and the West Sunbury Academy. In 1898 he graduated from the Medico Chirurgical College in Philadelphia, and immediately after established his office in Butler where he became one of the most prominent physicians in the county and where he practiced until the time of his death.

Dr. Atwell was a member of the First United Presbyterian Church and took an active interest in the affairs of the church, having been a member of the United Presbyterian Sessions since 1912.

He was an Associate Member of the Pittsburgh Academy of Medicine, a member of the Butler County Medical Society, the Pennsylvania State Society, a Fellow of the American Medical Association, and has been a Fellow of the American College of Physicians since 1912.

During the World War, Dr. Atwell was First Lieutenant in the Medical Corps of the U. S. Army.

Surviving are his widow, Mrs. Mollie Jennings Atwell; a daughter, Mrs. Charles Midberry of Butler; a son, Jennings Clinton Atwell, Jr., of Butler, and several brothers and sisters.

E. Bosworth McCready, M.D., F.A.C.P.,
Governor for Western Pennsylvania